

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



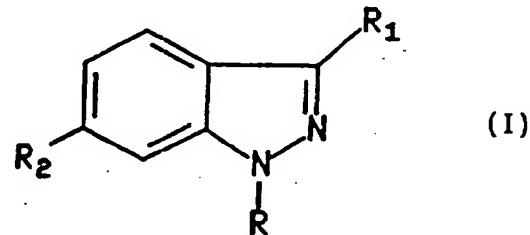
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 401/12, A61K 31/415, 31/44, C07D 409/04, 231/56	A1	(11) International Publication Number: WO 98/09961 (43) International Publication Date: 12 March 1998 (12.03.98)
(21) International Application Number: PCT/IB97/01023		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 25 August 1997 (25.08.97)		
(30) Priority Data: 60/025,446 4 September 1996 (04.09.96) US		
(71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).		
(72) Inventor; and		
(75) Inventor/Applicant (for US only): MARFAT, Anthony [US/US]; 333 Lantern Hill Road, Mystic, CT 06355 (US).		
(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).		

(54) Title: INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS OF PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)

(57) Abstract

The invention relates to compounds of formula (I) and pharmaceutically acceptable salts thereof, wherein R, R₁, and R₂, are as defined herein. The invention further relates to pharmaceutical compositions containing, and methods of using, the compounds of formula (I), or acceptable salts thereof, for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal. The invention also relates to intermediates that are useful in the preparation of the compounds of formula (I).



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Larvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KZ	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

5 INDAZOLE DERIVATIVES AND THEIR USE AS INHIBITORS OF PHOSPHODIESTERASE (PDE) TYPE IV AND THE PRODUCTION OF TUMOR NECROSIS FACTOR (TNF)

This invention relates to novel indazole analogs. The compounds are selective inhibitors of phosphodiesterase (PDE) type IV and the production of tumor necrosis factor (TNF), and as such are useful in the treatment of asthma, arthritis, bronchitis, chronic obstructive airway disease, psoriasis, allergic rhinitis, dermatitis, and other inflammatory diseases, central nervous system disorders such as depression and multi-infarc dementia, AIDS, septic shock and other diseases involving the production of TNF. This invention also relates to a method of using such compounds in the treatment of the foregoing diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

15 The following co-pending United States provisional patent applications also disclose and claim indazole derivatives that are selective inhibitors of PDE type IV and the production of TNF: United States provisional application number 60/021,072, filed June 27, 1996; United States provisional application number 60/020,385, filed June 25, 1996; and United States provisional application number 60/016,861, filed May 3, 1996.

20 The foregoing co-pending United States provisional patent applications are incorporated herein by reference in their entirety.

Since the recognition that cyclic adenosine phosphate (AMP) is an intracellular second messenger (E.W. Sutherland, and T. W. Rall, Pharmacol. Rev., 12, 265, (1960)), inhibition of the phosphodiesterases has been a target for modulation and, 25 accordingly, therapeutic intervention in a range of disease processes. More recently, distinct classes of PDE have been recognized (J. A. Beavo et al., Trends in Pharm. Sci. (TIPS), 11, 150, (1990)), and their selective inhibition has led to improved drug therapy (C. D. Nicholson, M. S. Hahid, TIPS, 12, 19, (1991)). More particularly, it has been recognized that inhibition of PDE type IV can lead to inhibition of inflammatory mediator 30 release (M. W. Verghese et al., J. Mol. Cell Cardiol., 12 (Suppl. II), S 61, (1989)) and airway smooth muscle relaxation (T.J. Torphy in "Directions for New Anti-Asthma Drugs," eds S.R. O'Donnell and C. G. A. Persson, 1988, 37 Birkhauser-Verlag). Thus, compounds that inhibit PDE type IV, but which have poor activity against other PDE types, would inhibit the release of inflammatory mediators and relax airway smooth 35 muscle without causing cardiovascular effects or antiplatelet effects. It has also been disclosed that PDE IV inhibitors are useful in the treatment of diabetes insipidus (Kidney Int. 37:362, 1990; Kidney Int. 35:494) and central nervous system disorders

-2-

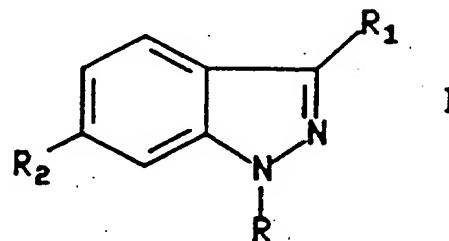
such as depression and multi-infarct dementia (PCT international application WO 92/19594 (published November 12, 1992)).

TNF is recognized to be involved in many infectious and auto-immune diseases (W. Fiers, *Fed. of Euro. Bio. Soc. (FEBS) Letters*, 285, 199, (1991)). Furthermore, it 5 has been shown that TNF is the prime mediator of the inflammatory response seen in sepsis and septic shock (C. E. Spooner *et al.*, *Clinical Immunology and Immunopathology*, 62, S11, (1992)).

Summary of the Invention

The present invention relates to compounds of the formula I

10



15

and to pharmaceutically acceptable salts thereof, wherein:

R is H, C₁-C₈ alkyl, -(CH₂)_m(5 to 10 membered heterocyclyl) wherein m is 0 to 2, (C₁-C₈ alkoxy)C₁-C₈ alkyl, C₂-C₈ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c 20 are independently 0 or 1, Z₁ is C₁-C₈ alkylene or C₂-C₈ alkenylene, and Z₂ is O, S, SO₂, or NR₁₂, and wherein said R groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, C₁-C₈ alkyl, C₂-C₈ alkenyl, C₁-C₈ alkoxy, trifluoromethyl, nitro, -CO₂R₁₂, -C(O)NR₁₂R₁₃, -NR₁₂R₁₃ and -SO₂NR₁₂R₁₃;

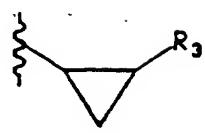
25 R₁ is H, C₁-C₈ alkyl, C₂-C₈ alkenyl, or phenyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

30 R₂ is R₁₀, -C(O)NR₁₂(CHR₁₂)_mC(O)NR₁₂O(CH₂)_q(C₆-C₁₀ aryl), -C(=NR₁₂)NH(CH₂)_p(C₆-C₁₀ aryl), -C(O)NR₁₂(CHR₁₂)_mC(O)NR₁₂(CH₂)_pOR₁₂, -C(O)NR₁₂(CHR₁₂)_mS(C₁-C₄ alkyl), -C(=NOC(O)R₂₀)R₂₀, -CR₁₇R₁₈CHR₂₀NR₁₂SO₂(CH₂)_pA, -CR₁₇R₁₈CHR₂₀NR₁₂P(O)(OR₁₂)C(O)(C₁-C₄ alkyl), -CR₁₇R₁₈CHR₂₀NR₁₂P(O)(C₁-C₄ alkoxy)₂, -Z₃R₇, or -(CR₁₇R₁₈)_mNR₁₂(C(O))_qR₁₀ wherein p is 0 to 2, m is 1 to 6, and q is 1 or 2;

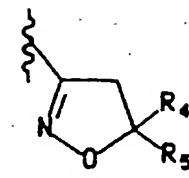
-3-

or R_2 is

5

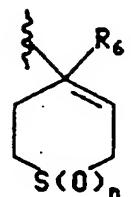


(Ia)

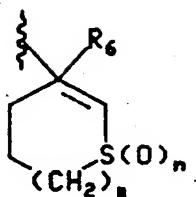


(Ib)

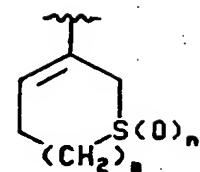
10



(Ic)

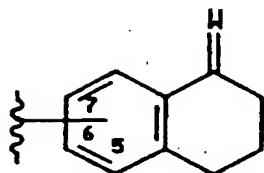


(Id)

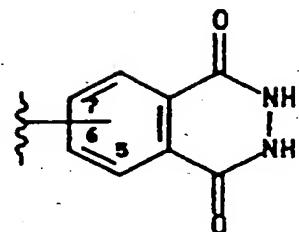


(Ie)

15



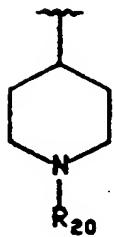
(If)



(Ig)

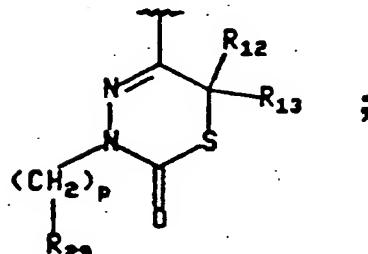
20

25



(Ih)

OR



(Ii)

30

wherein in said formulas (Ia)-(Ii), the structures of formulas (If) and (Ig) are attached to formula I at carbons 5, 6, or 7 of said formulas (If) and (Ig), the dashed line in formulas (Ic) and (Id) indicates a single bond or double bond, except R₄ is absent in formulas (Ic) and (Id) where said dashed line indicates a double bond, n is 0 to 2, p is

5 0 to 6, and m is 0 or 1;

R₃ is -C(O)N(CH₃)(OCH₃) or -(CH₂)_nOH wherein n is 0 to 4;

R₄ and R₅ are independently selected from the group consisting of H, ethyl, -CO₂H and -C(O)NHOH;

10 R₆ is H, cyano, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OC(O)(C₁-C₆ alkyl) or -OC(O)(C₆-C₁₀ aryl);

15 R₇ is C₆-C₁₀ aryl or 5 to 10 membered heterocyclyl, wherein said R₇ groups are optionally substituted by 1 to 3 substituents independently selected from halo, trifluoromethyl, cyano, nitro, -CO₂R₁₂, C₁-C₄ alkoxy, -OC(O)(C₁-C₄ alkyl), -NR₁₂C(O)(C₁-C₄ alkyl), -C(O)NH₂, -C(O)NHOH, -C(O)O(C₁-C₄ alkyl), C₁-C₄ alkyl, -S(O)_nR₁₂ wherein 20 n is 0 to 2, benzoyl, -NR₁₂R₁₃, -OR₁₂, C₁-C₆ alkanoyl, -Y₁-(C₆-C₁₀ aryl), -C(O)O(C₆-C₁₀ aryl), -NH(C₆-C₁₀ aryl), -C(O)NH(C₆-C₁₀ aryl), -C(O)NR₁₂O(CH₂)_n(C₆-C₁₀ aryl) wherein n is 1 to 3, and -SO₂NH(C₆-C₁₀ aryl);

25 R₈ is H, C₁-C₆ alkyl, or -(CH₂)_n(C₆-C₁₀ aryl) wherein n is 0 to 4;

R₉ is H, -OR₁₂, -(CH₂)_mA or -CH₂O(CH₂)_mA wherein m is 0 to 2;

30 R₁₀ is C₁-C₄ alkyl, -OR₁₂, -CR₁₂R₁₃OR₁₂, -CR₁₂R₁₃NR₁₂R₁₃, -CR₁₂(OR₁₂)CR₁₂R₁₃OR₁₂, 2,2-dimethyl-1,3-dioxolan-4-yl, -NR₁₂C(O)NR₁₂R₁₃, -S(CR₁₂R₁₃)_nCH₃ wherein n is 0 to 5, -NR₁₂(CH₂)_q(pyridyl) wherein q is 0 or 1, -P(O)(C₁-C₄ alkoxy)₂, -NR₁₂R₁₃, -NR₁₂OR₁₂, -NR₁₂NR₁₂R₁₁, -NR₁₂CH₂R₁₄, -OCH₂NR₁₂C(O)R₁₄, -OCH₂C(O)NR₁₂R₁₀, -OCHR₁₂OC(O)(C₁-C₄ alkyl), -OCHR₁₂C(O)(C₁-C₃ alkoxy), -O(CH₂)_mR₁₁, or -NR₁₂(CH₂)_mR₁₁ wherein m is 0 to 2;

R₁₁ is H or A;

each R₁₂ and R₁₃ is independently H or C₁-C₄ alkyl;

R₁₄ is methyl or phenyl;

R₁₅ is H, methyl, ethyl, or -CH₂CH₂OH;

35 R₁₆ is H, methyl, ethyl, -CH₂C(O)NH₂, or -CH₂CH₂OH;

each R₁₇ is independently H, hydroxy, cyano, halo, C₁-C₃ alkyl, C₁-C₃ alkoxy, -NR₁₂R₁₃, -C(O)OR₁₂, -C(O)R₁₂, -CH=CR₁₂R₁₃, -C=CR₁₂, -CH₂NR₁₂R₁₃, -CH₂OR₁₂.

-5-

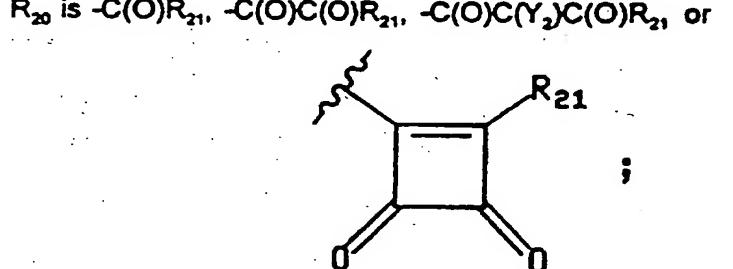
$-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{Y}_3)\text{H}$, or $-\text{CH}_2\text{NR}_{12}\text{C}(\text{O})\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, provided that when R_{17} is hydroxy then R_{18} is H or $\text{C}_1\text{-C}_4$ alkyl;

each R_{18} is independently H, fluoro, cyano, or $\text{C}_1\text{-C}_4$ alkyl, wherein said methyl is optionally substituted by 1 to 3 fluoro substituents;

5 or R_{17} and R_{18} are taken together to form an oxo (=O) moiety;

R_{19} is phenyl, naphthyl, pyrrolyl, furanyl, thienyl, oxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, or 5,6,7,8-tetrahydroisoquinolinyl, wherein said R_{19} groups, except said phenyl, are optionally substituted by 1 to 3 R_{23} substituents, and wherein said phenyl R_{19} group is optionally substituted by 1 to 3 substituents independently selected from R_{23} and R_{24} ;

10 R_{20} is $-\text{C}(\text{O})\text{R}_{21}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}_{21}$, $-\text{C}(\text{O})\text{C}(\text{Y}_3)\text{C}(\text{O})\text{R}_{21}$, or



R_{21} is H, $-\text{OR}_{22}$, $-\text{NHR}_{22}$, $-\text{NHOH}$, $-\text{NNNH}_2$, $-(\text{CH}_2)_n\text{Y}_3$ (phenyl) or $-(\text{CH}_2)_n\text{Y}_3$ (pyridyl) wherein n is 0 to 4;

20 R_{22} is H, $\text{C}_1\text{-C}_6$ alkyl, $-(\text{CH}_2)_n\text{Y}_3$ (phenyl) or $-(\text{CH}_2)_n\text{Y}_3$ (pyridyl) wherein n is 0 to 4;

each R_{23} is independently halo, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_7$ alkoxy, $\text{C}_2\text{-C}_6$ alkylenedioxy, trifluoromethyl, $-\text{NR}_{12}\text{R}_{13}$, nitro, $-\text{C}(\text{NR}_{12})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{NOR}_{12})\text{R}_{13}$, $-\text{C}(\text{NCN})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{NCN})\text{SR}_{12}$, $-(\text{CH}_2)_m\text{CN}$ wherein m is 0 to 3, hydroxy, $-\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{O})\text{NR}_{12}\text{OR}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{NR}_{12}\text{R}_{13}$, $-\text{OC}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$,

25 $-\text{CO}_2\text{R}_{13}$, $-\text{SO}_2\text{R}_{12}$, $-\text{SO}_2\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{SO}_2\text{R}_{13}$, or $-\text{NR}_{12}\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$;

each R_{24} is independently imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolidinyl, thiazolidinyl, or imidazolidinyl, wherein each of the foregoing R_{24} substituents is optionally substituted by 1 to 3 R_{23} substituents;

30 R_{25} is $-\text{NR}_{12}\text{R}_{13}$, $-\text{NH}(\text{C}_6\text{-C}_{10}$ aryl), $\text{C}_1\text{-C}_6$ alkoxy, or $\text{C}_6\text{-C}_{10}$ aryloxy;

R_{26} is H, $\text{C}_1\text{-C}_6$ alkyl or $-(\text{CH}_2)_m\text{Y}_3$ (phenyl) wherein m is 0 to 4 and the phenyl moiety of said $-(\text{CH}_2)_m\text{Y}_3$ (phenyl) R_{26} group is optionally substituted by halo, $-\text{OR}_{12}$, $\text{C}_1\text{-C}_6$ alkanoyloxy, $\text{C}_6\text{-C}_{10}$ aryloxy, $-\text{NR}_{12}\text{R}_{13}$, $-\text{NH}(\text{C}_6\text{-C}_{10}$ aryl), or $-\text{NHC}(\text{O})(\text{C}_1\text{-C}_4$ alkyl);

-6-

each R_{27} is independently halo, $-(CH_2)_pNR_{12}C(O)CH_3$, wherein p is 1 to 5, nitro, cyano, $-NR_{12}R_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-C(Y_1)NR_{12}R_{13}$, $-NR_{12}C(NCN)S(C_1-C_3$ alkyl), $-NR_{12}C(NCN)NR_{12}R_{13}$, $-NR_{12}C(O)NR_{12}R_{13}$, $-NR_{12}C(O)C(O)NR_{12}R_{13}$, $-C(=NR_{12})NR_{12}R_{13}$, $-S(O)_mCH_3$ wherein m is 0 to 2, $-C(=NR_{12})S(C_1-C_3$ alkyl), $-NR_{12}SO_2(C_1-C_3$ alkyl),

5 $-OC(O)R_{12}$, $-OC(O)NR_{12}R_{13}$, $-NR_{12}SO_2CF_3$, $-NR_{12}C(O)C(O)OR_{12}$, $-NR_{12}C(O)R_{12}$, $-NR_{12}C(O)OR_{12}$, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

R_{28} is H, fluoro, cyano, or C_1-C_2 alkyl, wherein said alkyl is optionally substituted by 1 to 3 substituents independently selected from halo, $-C(O)NR_{12}R_{13}$, and $-C(O)OR_{12}$;

10 R_{29} is phenyl optionally substituted by 1 or 2 substituents independently selected from $-NR_{12}R_{13}$, nitro, halo, $-OR_{12}$, $-NHR_{30}$, $-NR_{30}R_{31}$, and $-C(O)OR_{12}$;

each R_{30} and R_{31} is independently C_1-C_3 alkyl or C_2-C_3 alkenyl;

15 R_{32} is pyridin-4-yl optionally substituted by 1 or 2 substituents independently selected from halo and C_1-C_4 alkyl;

each A is independently C_1-C_6 alkyl, pyridyl, morpholinyl, piperidinyl, imidazolyl, thienyl, pyrimidyl, thiazolyl, triazolyl, quinolinylyl, phenyl, or naphthyl, wherein the foregoing A groups are optionally substituted with 1 to 3 R_{27} substituents, or A is $-(CH_2)_qS(C_1-C_4$ alkyl) wherein q is 1 or 2;

20 W is O, NOH, NNH_2 , $NOC(O)CH_3$, or $NNHC(O)CH_3$;

Y_1 is O or S;

25 Y_2 is O, NOH or H_2 ;

Y_3 is a bond or $-CH=CH-$;

Y_4 is a bond, O, S, or $-NH-$;

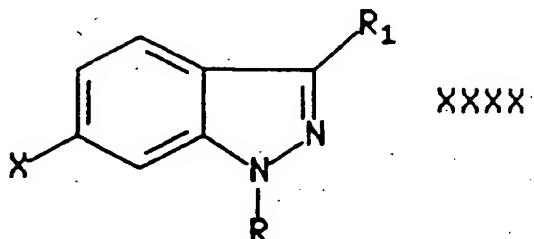
Y_5 is O, NR_{12} , NOR_{12} , NCN , $C(CN)_2$, $CR_{12}NO_2$, $CR_{12}C(O)OR_{12}$, $CR_{12}C(O)NR_{12}R_{13}$, $C(CN)NO_2$, $C(CN)C(O)OR_{12}$ or $C(CN)C(O)NR_{12}R_{13}$; and,

30 Z_3 is $-NR_{12}$, $-(CH_2)_n-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-CH_2C(Y_1)CH_2-$, $-CH=CH-$, $-C=C-$, $-CH(Y_1H)-$, $-C(Y_1)-$, $-CH_2C(Y_1)-$, $-C(Y_1)CH_2-$, $-C(Y_1)C(Y_1)-$, $-CH_2NR_{12}-$, $-CH_2-Y_1-$, $-C(Y_1)NR_6(CHR_{12})-$, $-NR_6C(Y_1)(CHR_{12})-$, $-NHCH_2-$, $-Y_1-CH_2-$, $-SOCH_2-$, $-CH_2SO-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-OC(Y_1)-$, $-N=N-$, $-NHSO_2-$, $-SO_2NH-$, $-C(Y_1)C(Y_1)NH-$, $-NHC(O)O-$, $-OC(O)NH-$ or $-NHC(O)NH-$, wherein in said Z_3 moieties n is 0 to 4 and m is 1 to 3.

-7-

The present invention also relates to compounds of the formula

5



and to pharmaceutically acceptable salts thereof, wherein R and R₁ are as defined above and X is -C(O)Cl. The compounds covered by the above formula are intermediates that are useful in the preparation of the compounds of formula I.

Specific compounds of formula I include those wherein R₂ is -Z₃-R, wherein Z₃ is -C(Y₁)NH-, -C(O)CH₂-, -NHC(Y₁)-, -Y₁-CH₂-, -OC(O)-, -CH=CH-, or -C(Y₁)C(Y₁)-, and R, is an optionally substituted aryl or heteroaryl group selected from phenyl, pyridyl, 15 pyrazinyl, thienyl, pyrimidinyl, 2,4-dioxopyrimidin-5-yl, isoxazolyl, isothiazolyl, pyridazinyl, and 1,2,4-triazinyl. More specifically, R, is substituted phenyl, 2,6-dihalo-substituted phenyl, or 3,5-dihalo-pyrid-4-yl.

Other specific compounds of formula I include those wherein R₂ is -Z₃-R, wherein Z₃ is -C(O)NH(CH₂)_n- or -NHC(O)(CH₂)_n-, wherein n is 0 or 1, and R, is phenyl or pyridyl optionally substituted by 1 to 3 substituents independently selected from halo, nitro, trifluoromethyl, -CO₂CH₃, methyl, methoxy, and -C(O)NH₂.

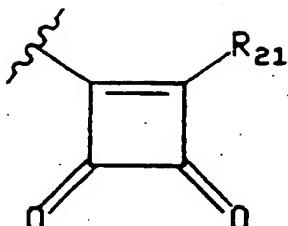
Other specific compounds of formula I include those wherein R₂ is -Z₃-R, wherein Z₃ is -C(O)NH- and R, is phenyl or pyridyl optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, cyano, carboxy 25 and -OC(O)C₁-C₄ alkyl.

Other specific compounds of formula I include those wherein R₂ is R₁₉ wherein R₁₉ is optionally substituted pyrimidinyl or optionally substituted pyridazinyl.

Other specific compounds of formula I include those wherein R₂ is a substituent of formula (Ih) wherein R₂₀ is -C(O)R₂₁, -C(O)C(O)R₂₁, or

-8-

5



wherein R_{21} is $-OR_{22}$, $-NHR_{22}$, or $-NHOH$, and R_{22} is H, C₁-C₃ alkyl, benzyl or pyridylmethyl.

Other specific compounds of formula I include those wherein R_2 is phenyl substituted by R_{24} wherein said R_{24} is oxadiazolyl, thiadiazolyl or tetrazolyl wherein said R_{24} groups are optionally substituted by C₁-C₂ alkyl, or wherein R_2 is phenyl substituted by cyanomethyl, hydroxy or formyl.

Other specific compounds of formula I include those wherein R_2 is $-Z_3R$, wherein Z_3 is $-C(Y_1)NH-$, and R is phenyl, pyrazinyl, pyrimidinyl, isoxazolyl, or pyridyl, wherein each of said R groups is optionally substituted by 1 to 3 substituents independently selected from halo, methoxycarbonyl, trifluoromethyl, benzoyl, acetyl, dimethylamino, hydroxy, nitro, methyl, cyano, methylsulphonyl, and methylthio.

Other specific compounds of formula I include those wherein R_2 is $-C(=NOC(O)R_{25})R_{26}$ wherein R_{25} is amino and R_{26} is H, C₁-C₃ alkyl or $-(CH_2)_m$ (phenyl) wherein m is 1 to 4 and said phenyl moiety is optionally substituted by halo, hydroxy, acetoxy, amino or acetamido.

Other specific compounds of formula I include those wherein R_2 is $-(CR_{17}R_{18})_mNR_q(C(O))_qR_{19}$ wherein m is 2, q is 2, each R_{17} is independently H, cyano or methyl, each R_{18} is independently H or methyl, R_q is H or methyl, and R_{19} is amino, hydroxy, methoxy or hydroxyamino.

Other specific compounds of formula I include those wherein R_2 is $-(CR_{17}R_{18})_mNR_q(C(O))_qR_{19}$ wherein m is 2, q is 1, each R_{17} is independently H, $-C(O)NH_2$, $-C=CH$, cyano, formyl, hydroxymethyl, or trifluoromethyl, each R_{18} is independently H or cyano, and R_{19} is C₁-C₄ alkyl.

Other specific compounds of formula I include those wherein R_2 is a substituent of formula (Ic), (Id) or (Ie), wherein, in formulas (Ic) and (Id), R_6 is H, hydroxy, C₁-C₃ alkyl or C₁-C₄ alkoxy.

-9-

Other specific compounds of formula I include those wherein R_2 is $-C(O)NR_9(CHR_{12})_mC(O)NR_{12}(CH_2)_pOR_{12}$ or $-C(O)NR_{12}(CHR_{12})_mS(C_1-C_4\text{ alkyl})$, wherein R_9 , R_{12} , m and p are as defined above.

Specific compounds of formula I include those selected from the group 5 consisting of:

- 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
- 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2,6-dichloro-phenyl)-amide;
- 1-Cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
- 3-Ethyl-1-isopropyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
- 10 1-Cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
- 1-Cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
- 3-Ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-15 4-yl)-amide;
- 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethyl-amide;
- 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-methylsulfanyl-ethyl)-amide;
- 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethyl-methyl amide;
- 20 S-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-benzyloxycarbamoyl-ethyl)-amide;
- R-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-hydroxycarbamoyl-ethyl)-amide; 1-Cyclopentyl-3-ethyl-8-thiophen-2-yl-1H-indazole; 1-Cyclopentyl-3-ethyl-6-phenyl-1H-indazole; and the pharmaceutically acceptable salts of the foregoing 25 compounds.

The present invention further relates to a pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) comprising a pharmaceutically effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

The present invention further relates to a method for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) by

-10-

administering to a patient an effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt thereof.

The present invention further relates to a pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, diabetes insipidus, autoimmune diabetes, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, dermatitis, depression or multi-infant dementia, comprising a pharmaceutically effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt, thereof together with a pharmaceutically acceptable carrier.

The present invention further relates to a method of treating or preventing the foregoing specific diseases and conditions by administering to a patient an effective amount of a compound according to formula I, as defined above, or a pharmaceutically acceptable salt thereof.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, 25 chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties. It is to be understood that where cyclic moieties are intended, at least three carbons in said alkyl must be present. Such cyclic moieties include cyclopropyl, cyclobutyl, cyclopentyl, 30 cyclohexyl and cycloheptyl.

The term "alkoxy", as used herein, unless otherwise indicated, includes -O-alkyl groups wherein alkyl is as defined above.

-11-

The term "alkanoyl", as used herein, unless otherwise indicated, includes -C(O)-alkyl groups wherein alkyl is as defined above.

The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as 5 phenyl or naphthyl.

The term "5 to 10 membered heterocycl", as used herein, unless otherwise indicated, includes aromatic and non-aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused 10 ring systems and ring systems substituted with one or more oxo moieties. An example of a 5 membered heterocyclic group is thiazolyl, and an example of a 10 membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, 15 pyrazinyl, tetrazolyl, furyl, thieryl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include benzimidazolyl.

The term "heteroaryl", as used herein, unless otherwise indicated, includes aromatic heterocyclic groups wherein heterocyclic is as defined above.

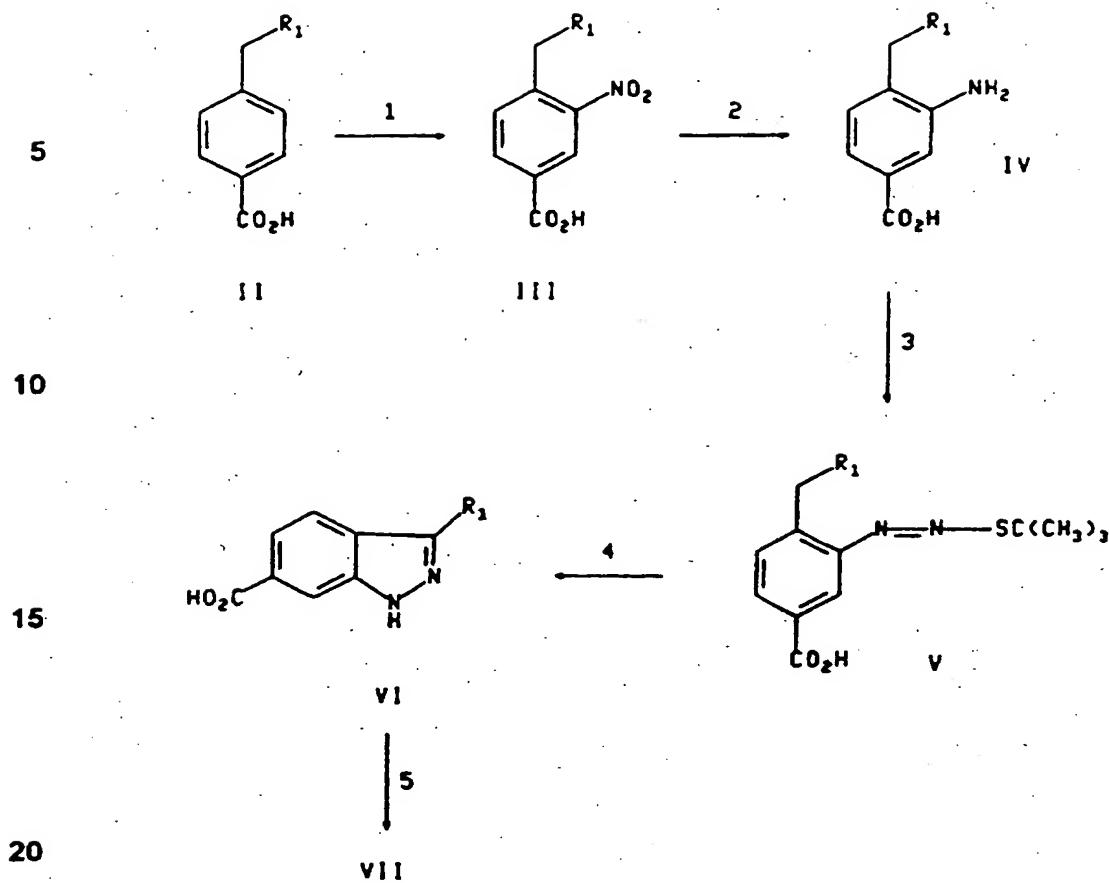
The phrase "pharmaceutically acceptable salt(s)", as used herein, unless 20 otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of formula I.

Certain compounds of formula I may have asymmetric centers and therefore 25 exist in different enantiomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of formula I and mixtures thereof. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

Detailed Description of the Invention

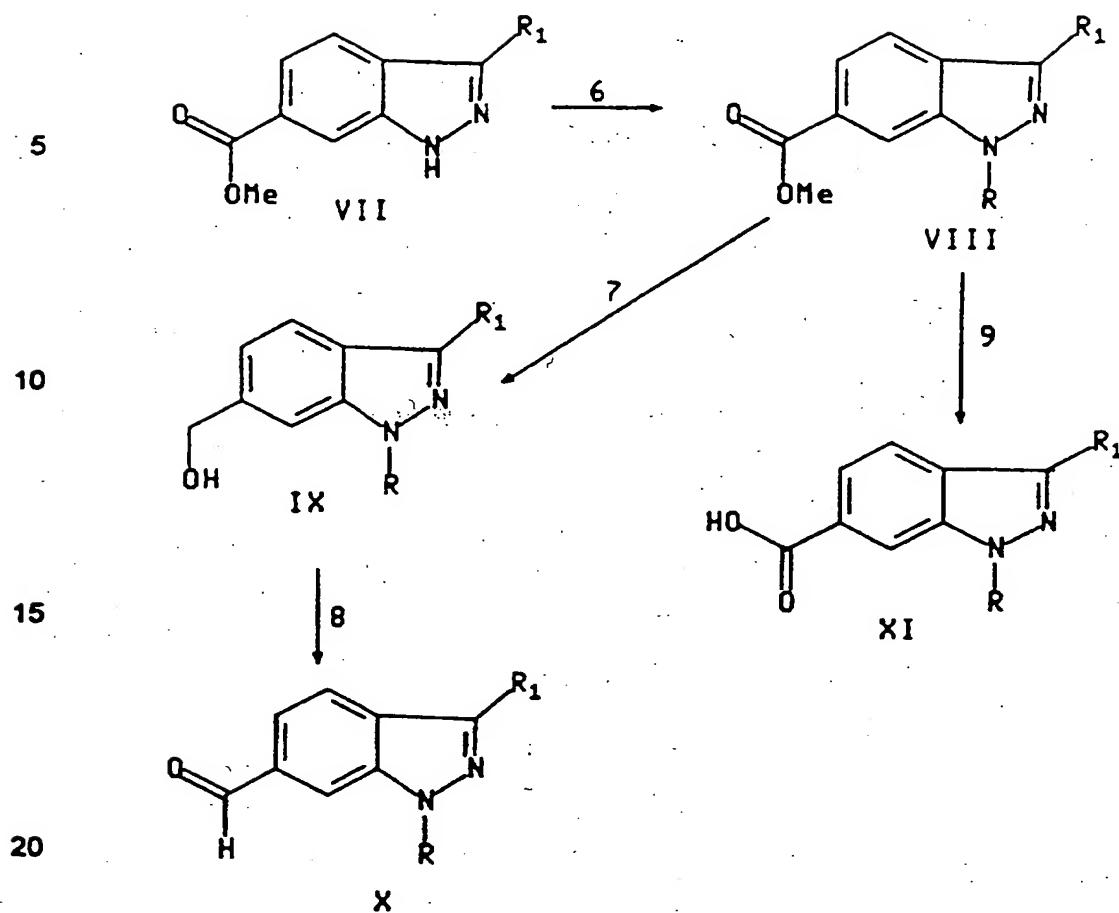
The following reaction Schemes 1-8 illustrate the preparation of the compounds 30 of the present invention. In the following Schemes, unless otherwise indicated, R, R₁, R₂, and R₁₂ are as defined above. In the following Schemes, "Me" means methyl and "Ph" means phenyl.

-12-

Scheme 1

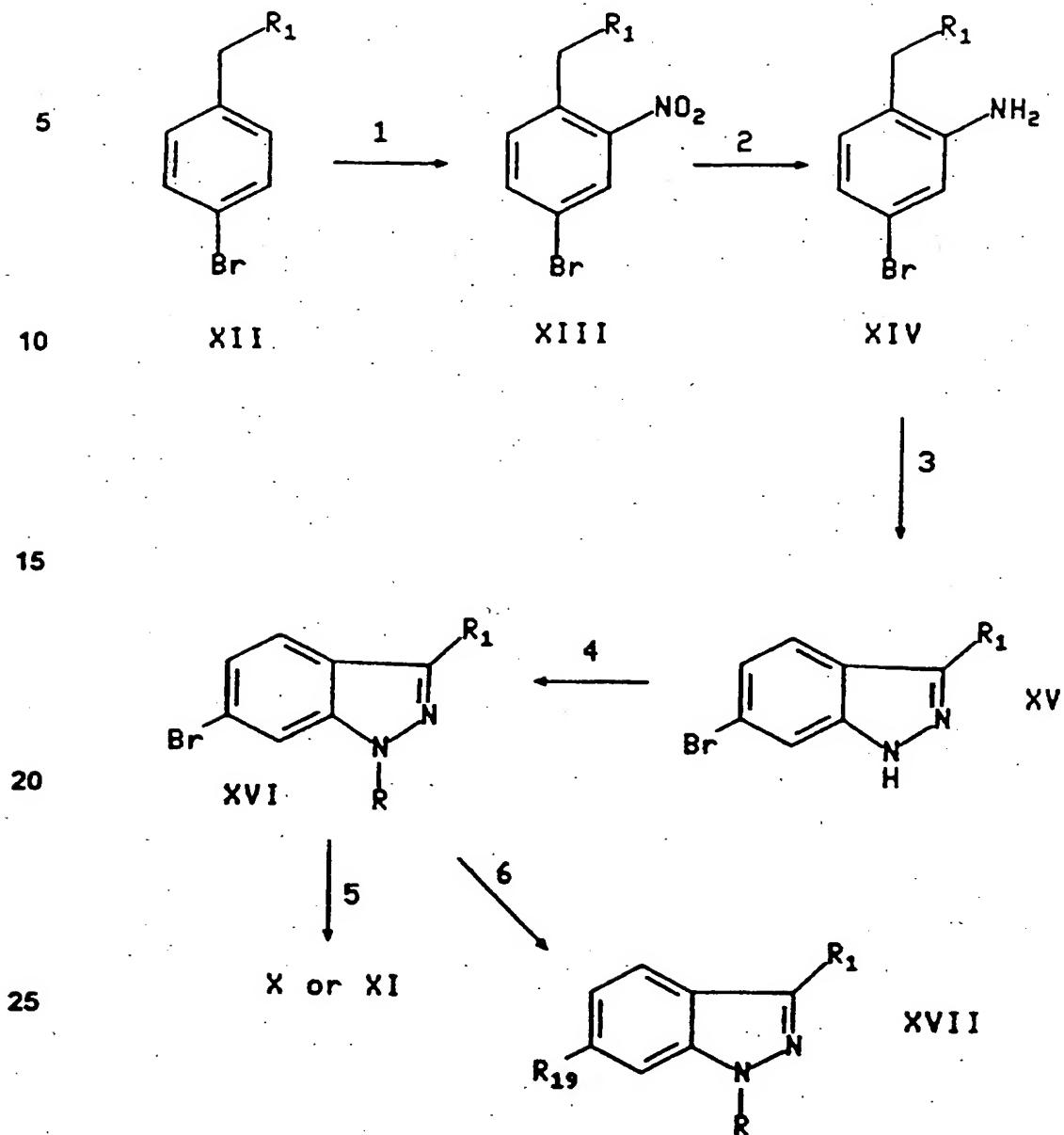
-13-

Scheme 1 continued



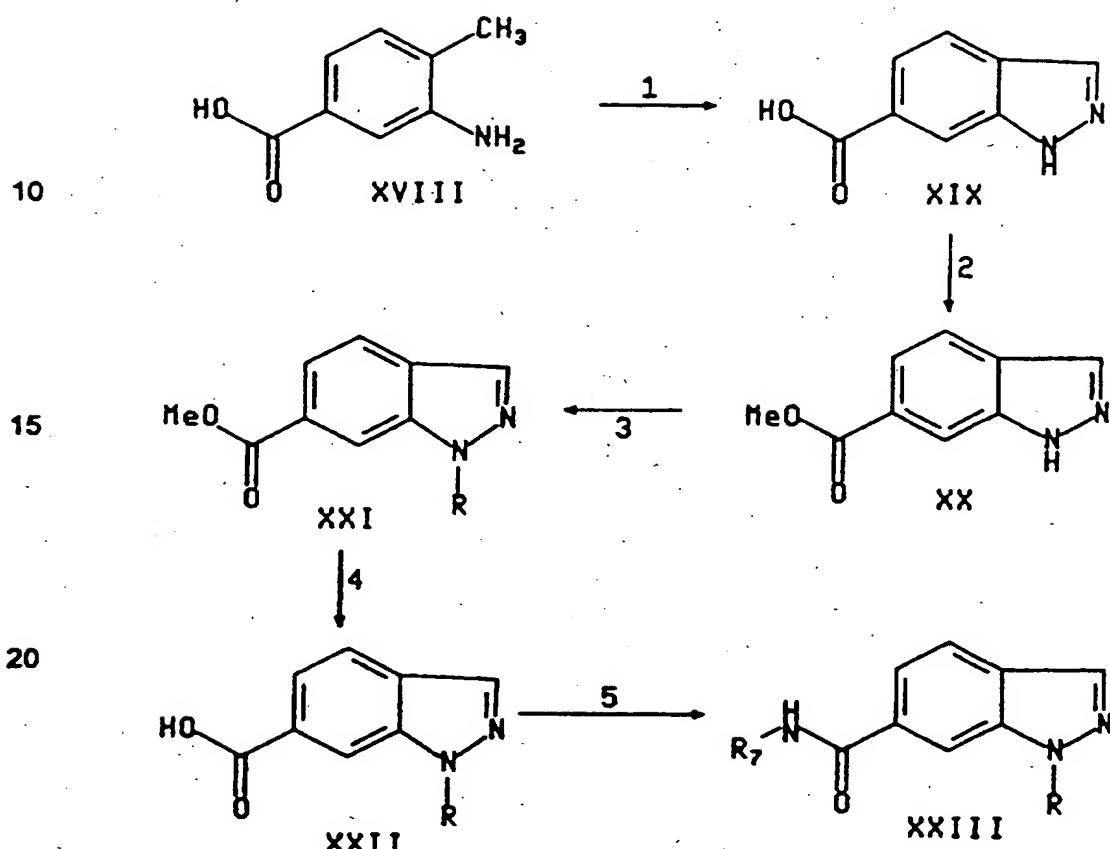
-14-

Scheme 2



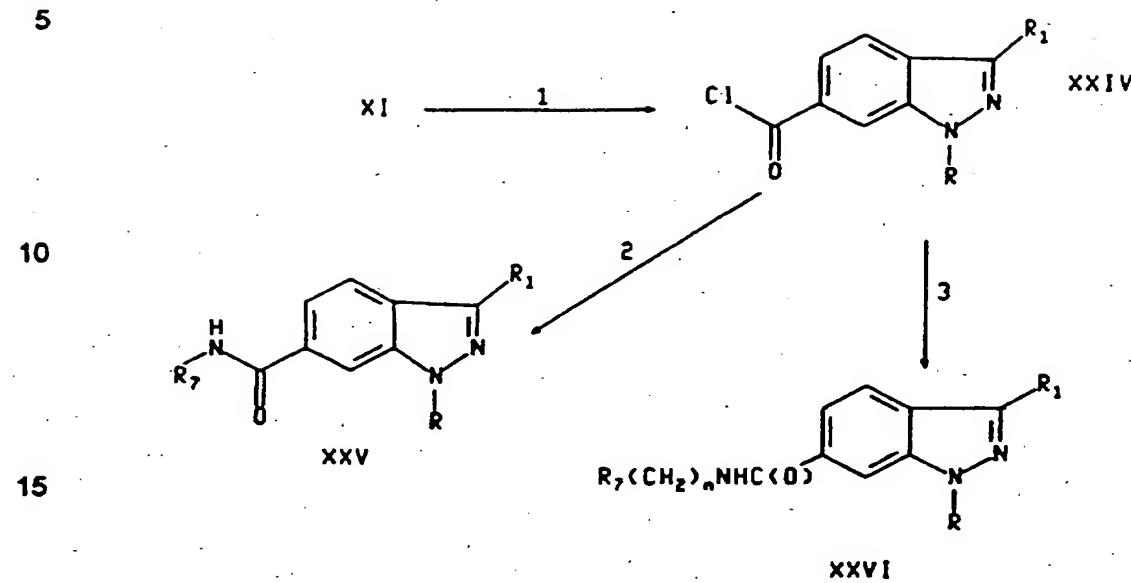
-15-

Scheme 3



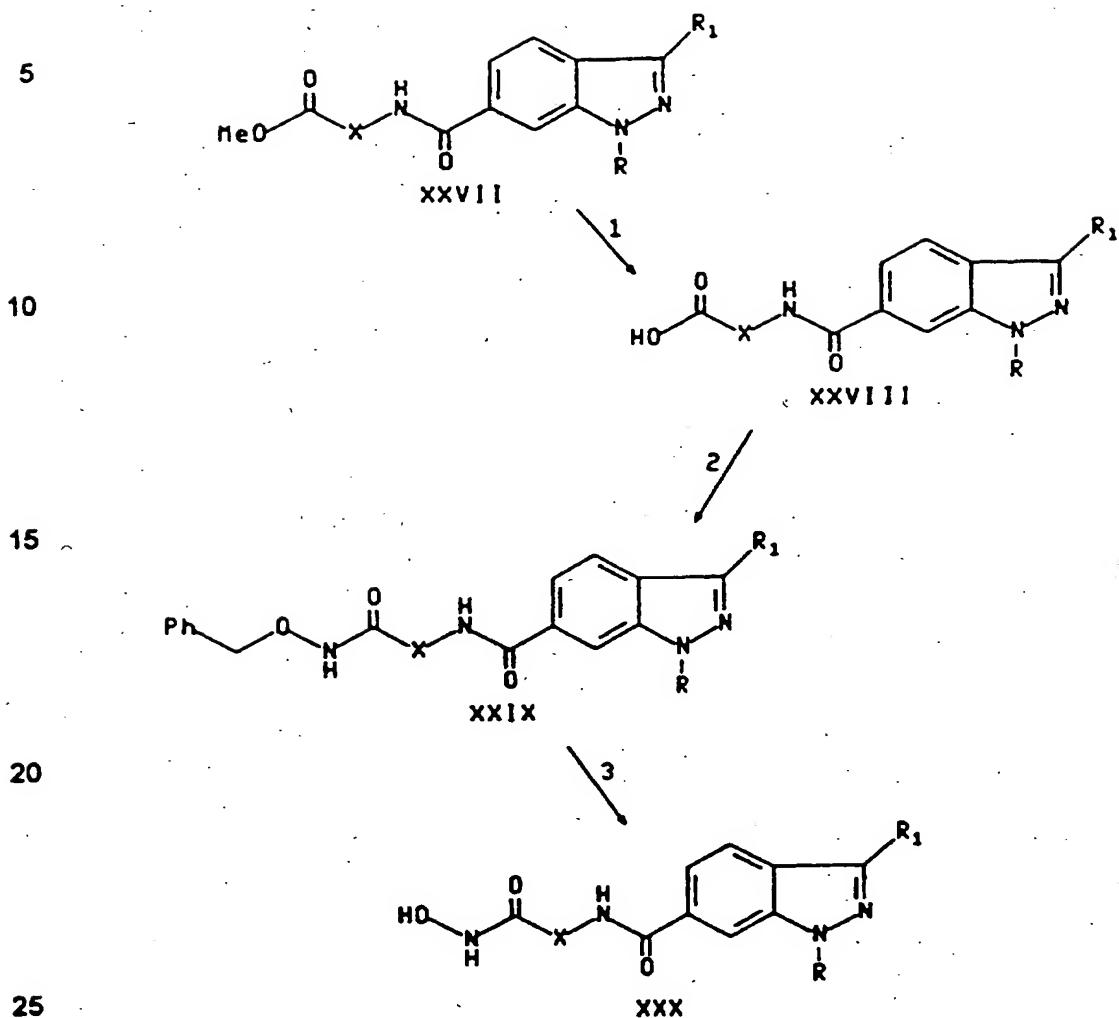
25

-16-

Scheme 4

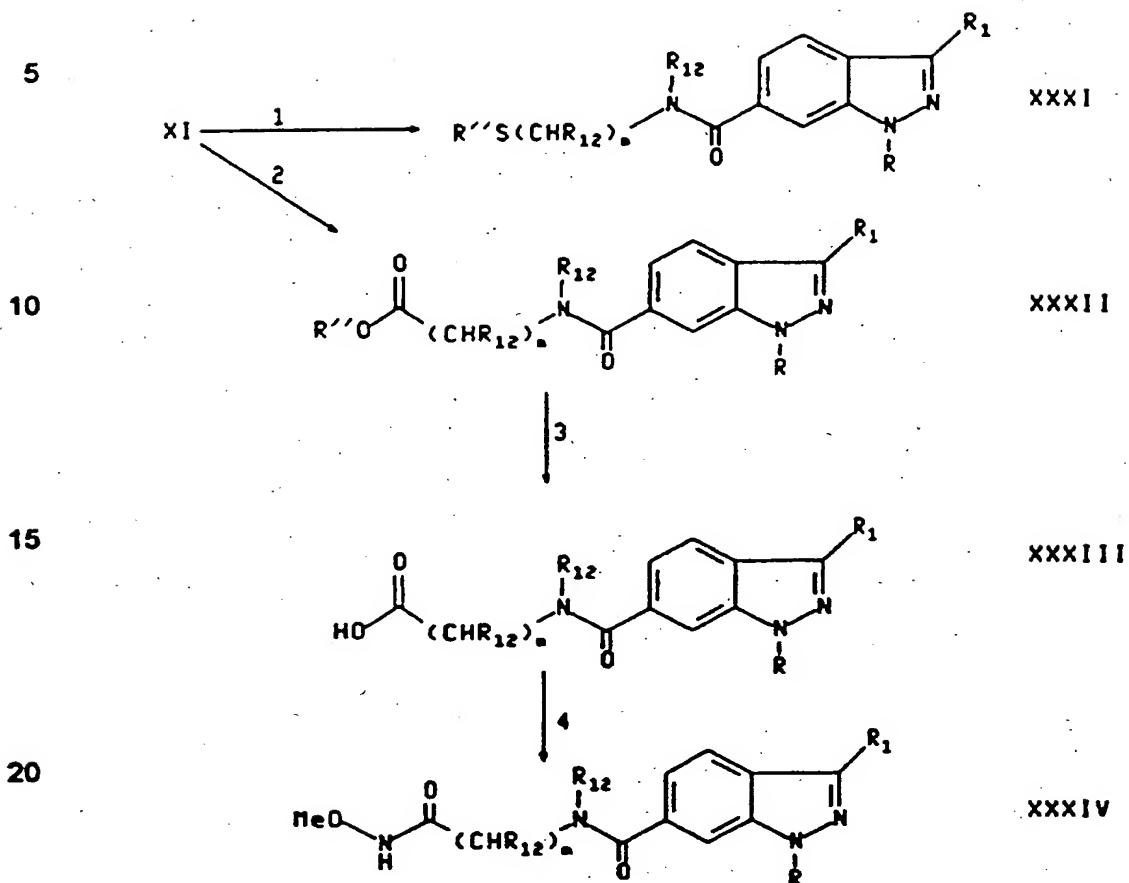
-17-

Scheme 5



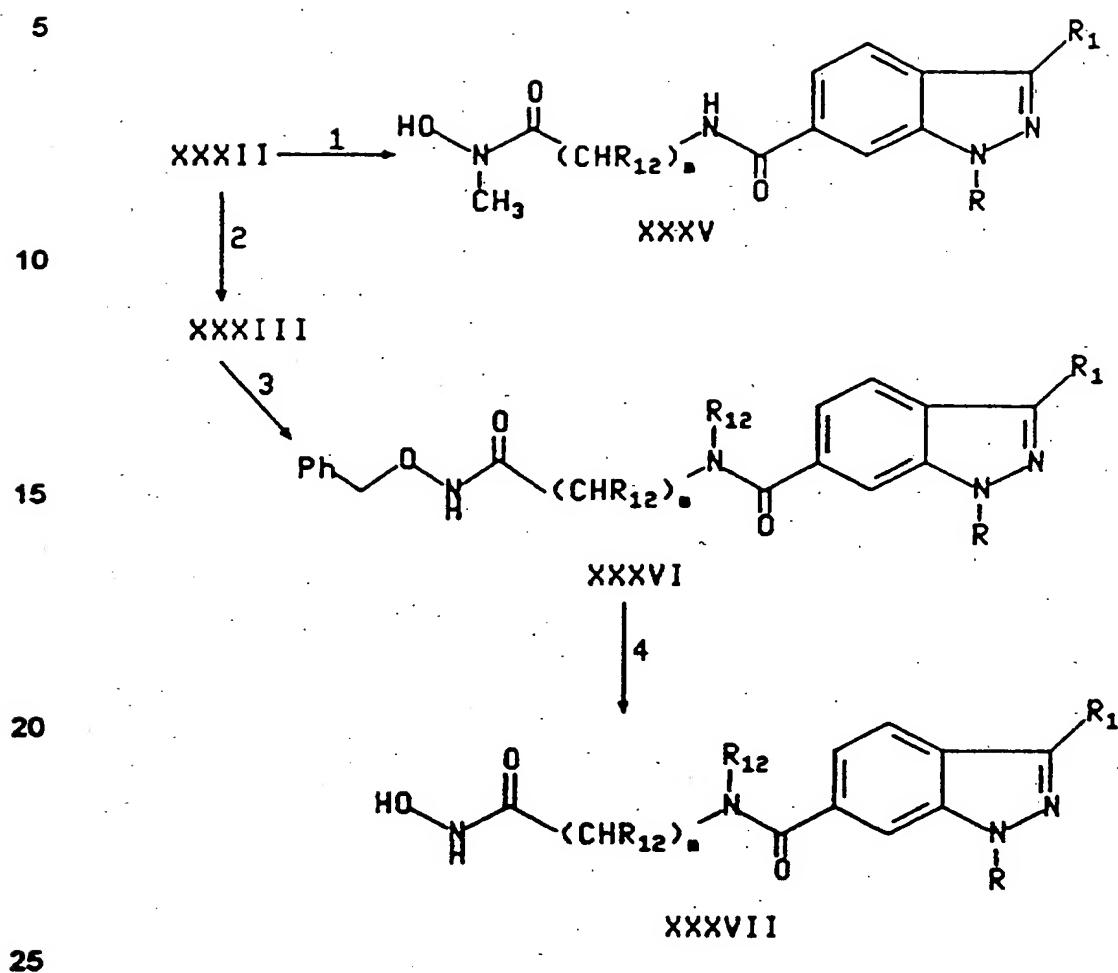
-18-

Scheme 6



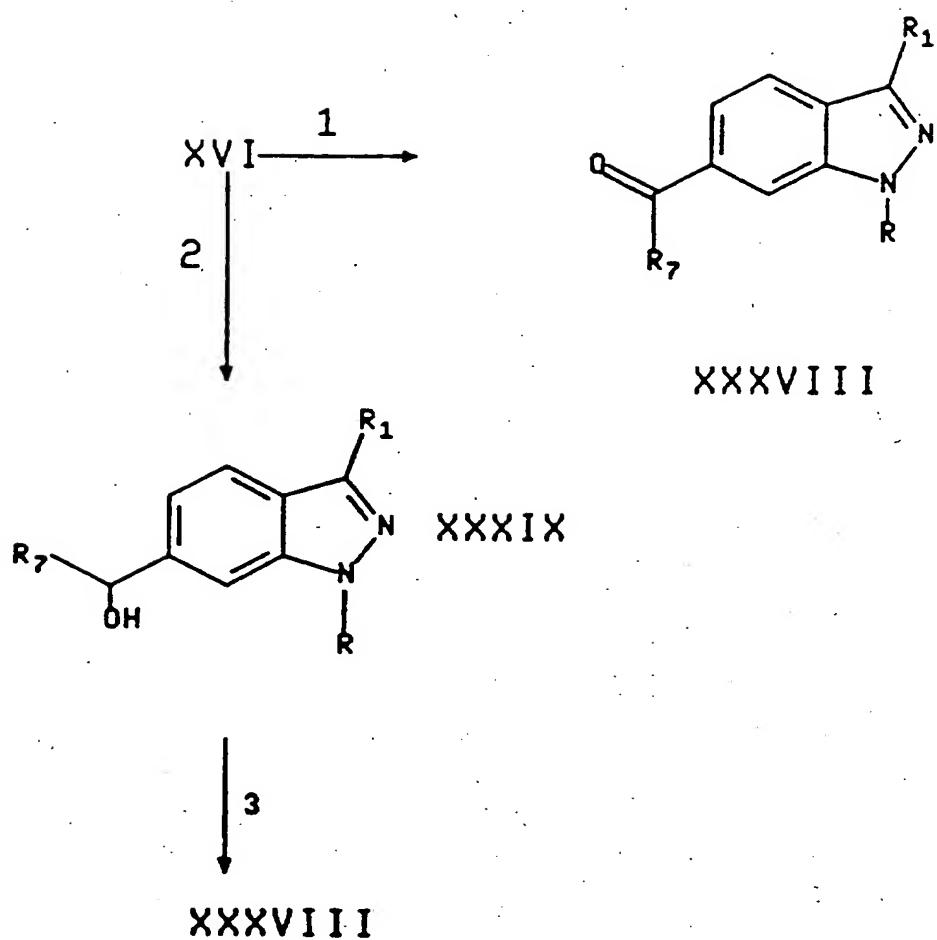
25

-19-

Scheme 7

-20-

Scheme 8



The preparation of compounds of formula I can be carried out by one skilled in the art according to one or more of the synthetic methods outlined in Schemes 1-8 above and the examples referred to below. In step 1 of Scheme 1, the carboxylic acid of formula II, which is available from known commercial sources or can be prepared 5 according to methods known to those skilled in the art, is nitrated under standard conditions of nitration ($\text{HNO}_3/\text{H}_2\text{SO}_4$, 0°C) and the resulting nitro derivative of formula III is hydrogenated in step 2 of Scheme 1 using standard hydrogenation methods (H_2 -Pd/C under pressure) at ambient temperature (20-25°C) for several hours (2-10 hours) to provide the compound of formula IV. In step 3 of Scheme 1, the amino benzoic acid 10 of formula IV is reacted with a base such as sodium carbonate under aqueous conditions and gently heated until mostly dissolved. The reaction mixture is chilled to a lower temperature (about 0°C) and treated with sodium nitrate in water. After about 15 minutes, the reaction mixture is slowly transferred to an appropriate container holding crushed ice and a strong acid such as hydrochloric acid. The reaction mixture 15 is stirred for 10-20 minutes and then added, at ambient temperature, to a solution of excess t-butyl thiol in an aprotic solvent such as ethanol. The reaction mixture is acidified to a pH of 4-5 through addition of an inorganic base, preferably saturated aqueous Na_2CO_3 , and the reaction mixture is allowed to stir at ambient temperature for 1-3 hours. Addition of brine to the reaction mixture, followed by filtration, provides the 20 sulfide of formula V.

In step 4 of Scheme 1, the sulfide of formula V is converted to the corresponding indazole carboxylic acid of formula VI by reacting the sulfide of formula V with a strong base, preferably potassium t-butoxide, in dimethyl sulfoxide (DMSO) at ambient temperature. After stirring for several hours (1-4 hours), the reaction mixture 25 is acidified with a strong acid, such as hydrochloric or sulfuric acid, and then extracted using conventional methods. In step 5 of Scheme 1, the indazole carboxylic acid of formula VI is converted to the corresponding ester of formula VII by conventional methods known to those skilled in the art. In step 6 of Scheme 1, the compound of formula VIII is provided through alkylation of the ester of formula VII by subjecting the 30 ester to conventional alkylation conditions (strong base/various alkylating agents and, optionally, a copper catalyst such as CuBr_2) in a polar aprotic solvent, such as tetrahydrofuran (THF), N-methylpyrrolidinone or dimethylformamide (DMF), at ambient or higher temperature (25-200°C) for about 6-24 hours, preferably about 12 hours. In

step 7 of Scheme 1, the compound of formula VIII is converted to the corresponding alcohol of formula IX by following conventional methods known to those skilled in the art for reducing esters to alcohols. Preferably, the reduction is effected through use of a metal hydride reducing agent, such as lithium aluminum hydride, in a polar aprotic solvent at a low temperature (about 0°C). In step 8 of Scheme 1, the alcohol of formula IX is oxidized to the corresponding aldehyde of formula X according to conventional methods known to those skilled in the art. For example, the oxidation can be effected through use of a catalytic amount of tetrapropylammonium perrutenate and excess N-methylmorpholine-N-oxide, as described in J. Chem. Soc., Chem. Commun., 10 1625 (1987), in an anhydrous solvent, preferably methylene chloride. In step 9 of Scheme 1, the ester of formula VIII is converted to the corresponding acid of formula XI by methods known to those skilled in the art, such as by treating the starting compound with sodium hydroxide in methanol and heating the mixture to reflux for several hours (2 or more hours). The acid of formula XI, like the aldehyde of formula X, is a useful intermediate for the preparation of various compounds of formula I.

Scheme 2 illustrates an alternative method of preparing the aldehyde of formula X and the acid of formula XI, as well as a method of preparing the compound of formula XVII. In step 1 of Scheme 2, the compound of formula XII is nitrated using conventional nitration conditions (nitric and sulfuric acid) to provide the compound of formula XIII. In step 2 of Scheme 2, the nitro derivative of formula XIII is reduced to the corresponding amine of formula XIV according to conventional methods known to those skilled in the art. Preferably, the compound of formula XIII is reduced to the amine of formula XIV using anhydrous stannous chloride in an anhydrous aprotic solvent such as ethanol. In step 3 of Scheme 2, the amine of formula XIV is converted to the corresponding indazole of formula XV by preparing the corresponding diazonium tetrafluoroborates as described in A. Roe, Organic Reactions, Vol. 5, Wiley, New York, 1949, pp. 198-206, followed by phase transfer catalyzed cyclization as described in R. A. Bartsch and I. W. Yang, J. Het. Chem. 21, 1083 (1984). In step 4 of Scheme 2, alkylation of the compound of formula XV is performed using standard methods known to those skilled in the art (i.e. strong base, polar aprotic solvent and an alkyl halide) to provide the N-alkylated compound of formula XVI. In step 5 of Scheme 2, the compound of formula XVI is subjected to metal halogen exchange employing an alkyl lithium, such as n-butyl lithium, in a polar aprotic solvent, such as THF, at low

temperature (-50°C - 100°C (-78°C preferred)) followed by quenching with DMF at low temperature and warming to ambient temperature to provide the aldehyde intermediate of formula X, or the mixture containing the compound of formula XVI is quenched with CO₂, warmed to ambient temperature, and then quenched with an acid, such as 5 hydrochloric acid, to provide the acid of formula XI. In step 6 of Scheme 2, the compound of formula XVI is converted to a compound of formula I wherein R₂ is R₁₉, which, as defined above, represents an aryl, heteroaryl, or heterocyclic moiety. In step 10 of Scheme 2, the compound of formula XVII is prepared by reacting the compound of formula XVI with a compound of formula R₁₉-B(OH)₂, wherein R₁₉ is as defined above, in the presence of Pd(PPh₃)₄ in aqueous Na₂CO₃ at reflux for about 4 hours.

Scheme 3 illustrates the preparation of a compound of formula I wherein R₁ is H and R₂ is -C(O)NHR, wherein R₇ is as defined above. In step 1 of Scheme 3, the compound of formula XVIII is treated with boron trifluoride etherate in ethanol-free chloroform at a temperature of about -20°C. After a short period, such as about 5 15 minutes, t-butyl nitrite is added to the mixture and the reaction is stirred at about 0°C for about 2 hours. Potassium acetate followed by 18-crown-6 are then added to provide the compound of formula XIX (1H-indazole-6-carboxylic acid). In step 2 of Scheme 3, the compound of formula XIX is treated with concentrated sulfuric acid in methanol at reflux for about 8 hours followed by stirring at ambient temperature for 20 about 18 hours to provide the compound of formula XX. In step 3 of Scheme 3, the compound of formula XX is reacted with a compound of the formula R-X, wherein R is as defined above and X is a leaving group such as chloro, bromo, or iodo, preferably bromo, in the presence of sodium hydride in DMF for about 10-24 hours, preferably 24 hours, at ambient temperature to provide the ester of formula XXI. In step 4 of Scheme 25 3, the ester of formula XXI is converted to the acid of formula XXII in accord with the procedure of step 9 of scheme 1. In step 5 of Scheme 3, the compound of formula XXII is treated with thionyl chloride and DMF (as a catalyst) in anhydrous toluene at reflux for about 3 hours to provide the corresponding acid chloride. Separately, a compound of the formula R₇NH₂, wherein R₇ is as defined above, is added to a mixture 30 of sodium hydride in anhydrous THF which is cooled to a temperature of about 0°C. To this second mixture, the acid chloride, referred to above, in THF is added and the mixture is stirred at ambient temperature for a period of 4-24 hours to provide the compound of formula XXIII.

Scheme 4 illustrates the preparation of compounds of formula I wherein R₂ is -C(O)NHR, or -C(O)NH(CH₂)_nR₇, wherein n is 1 to 4, and R₇ is as defined above. In step 1 of Scheme 4, the acid of formula XI is converted to the corresponding acid chloride of formula XXIV by treating the starting compound with thionyl chloride and 5 DMF (as a catalyst) in anhydrous toluene at reflux for about 3 hours. The acid chloride of formula XXIV can be converted to the compound of formula XXV by reacting the starting compound with a compound of the formula R₇NH₂, wherein R₇ is as defined above, in the presence of sodium hydride in anhydrous THF at a temperature of about 10 0°C, followed by warming to ambient temperature, for a period of 4-24 hours. This method is preferred where R₇ is substituted or unsubstituted pyridinyl. In the alternative, the compound of formula XXIV can be converted to the compound of formula XXV by reacting the starting compound with a compound of the formula R₇NH₂, wherein R₇ is as defined above, in the presence of sodium hydride in anhydrous DMF at ambient temperature for a period of 4-24 hours. This method is preferred 15 where R₇ is substituted or unsubstituted pyrimidinyl. In the alternative, the compound of formula XXIV can be converted to the compound of formula XXV by adding a compound of the formula R₇NH₂, wherein R₇ is as defined above, to the reaction mixture in which the acid chloride is prepared and then heating the mixture to a temperature of about 200°C for a short period, such as about 15 minutes.

20 In step 3 of Scheme 4, the compound of formula XXIV is converted to the compound of formula XXVI, wherein n is 1 to 4 and R₇ is as defined above, by reacting the starting compound with a compound of the formula H₂N-C(O)NH(CH₂)_nR₇, wherein n is 1 to 4, and R₇ is as defined above, in the presence of triethylamine, and optionally dimethylaminopyridine (DMAP), in methylene chloride 25 at ambient temperature for about 10-48 hours. In the alternative, the compound of formula XXIV can be converted to the compound of formula XXVI by reacting the starting compound with a compound of the formula H₂N-(CH₂)_nR₇, wherein n is 1 to 4, and R₇ is as defined above, in anhydrous pyridine at about 40°C for about 1 hour. This alternative method for step 3 of Scheme 4 is preferred where R₇ is a nitrogen-30 containing heterocyclic moiety such as pyridinyl.

Scheme 5 illustrates the preparation of compounds of formula I wherein R₂ is -Z₃R, wherein Z₃ is -C(O)NH- and R₇ is aryl, such as phenyl or naphthyl, substituted by -C(O)NHOH. Scheme 5 begins with a compound of the formula XXVII, wherein X

is an aryl moiety, as the starting material. The compound of formula XXVII is prepared according to the method illustrated in Scheme 4. In step 1 of Scheme 5, the compound of formula XXVII is hydrolyzed to the corresponding acid of formula XXVIII which can be done according to methods known to those skilled in the art, such as by treating the 5 compound of formula XXVII with sodium hydroxide in methanol at reflux for about 30 minutes to 1 hour. In step 2 of Scheme 5, the acid of formula XXVIII is converted to the compound of formula XXIX by treating the acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and O-benzylhydroxylamine hydrochloride in methylene chloride at ambient temperature for about 4-24 hours. In step 3 of Scheme 5, the 10 compound of formula XXIX is converted to the compound of formula XXX by treating the starting compound with 10% Pd/C in ethyl acetate and methanol under an H₂ atmosphere (about 30 psi) at ambient temperature for about 30 minutes to 1 hour.

Scheme 6 illustrates the preparation of compounds of formula I wherein R₂ is -C(O)NR₁₂(CHR₁₂)_mSR" (compound of formula XXXI), wherein R" is C₁-C₄ alkyl, m is 1 15 to 6, and R₁₂ is as defined above, or wherein R₂ is -C(O)NR₁₂(CHR₁₂)_mC(O)NHOMe (compound of formula XXXIV), wherein R₁₂ is as defined above, m is 1 to 6, and Me is methyl. In step 1 of Scheme 6, the compound of formula XI is treated with a compound of the formula H₂N-(CHR₁₂)_mSR", wherein R", R₁₂ and m are as defined above, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and triethylamine 20 in methylene chloride at ambient temperature for a period of about 18 hours to provide the compound of formula XXXI. In step 2 of Scheme 6, the compound of formula XXXII is prepared in accord with the method illustrated in Scheme 4. In step 3 of Scheme 6, the compound of formula XXXIII is prepared by heating to reflux the compound of formula XXXII in ethanol or methanol and sodium hydroxide for about 1 hour. In step 25 4 of Scheme 6, the compound of formula XXXIV is prepared by treating the compound of formula XXXIII with methoxylamine hydrochloride, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1-hydroxybenzotriazole hydrate and triethylamine in methylene chloride at ambient temperature for a period of about 18 hours.

Scheme 7 illustrates the preparation of compounds of formula I wherein R₂ is 30 -C(O)NH(CHR₁₂)_mC(O)N(CH₃)OH (compound of formula XXXV), wherein m is 1 to 6, or wherein R₂ is -C(O)NR₁₂(CHR₁₂)_mC(O)NHOH (compound of formula XXXVII), wherein R₁₂ is as defined above and m is 1 to 6. In step 1 of Scheme 7, the compound of formula XXXV is prepared by treating the compound of formula XXXII with sodium and

N-methylhydroxylamine hydrochloride in methanol at ambient temperature for about 16 hours. In step 2 of Scheme 7, the compound of formula XXXIII is prepared in accord with step 3 of Scheme 6. In step 3 of Scheme 7, the compound of formula XXXVI is prepared by treating the compound of formula XXXIII with O-benzylhydroxylamine, 1-hydroxybenzotriazole hydrate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and triethylamine in methylene chloride at ambient temperature for a period of about 18 hours. In step 4 of Scheme 7, the compound of formula XXXVII is prepared by treating the compound of formula XXXVI with 10% Pd/C in methanol and ethyl acetate under a H₂ atmosphere (about 30 psi) at ambient temperature for about 10 30 minutes to 1 hour.

Scheme 8 illustrates the preparation of compounds of formula XXXVIII. In step 1 of Scheme 8, the compound of formula XVI, which is prepared according to the method of Scheme 2, is treated with n-butyl lithium in anhydrous THF at a low temperature, such as about -78°C, for about 30 minutes, followed by quenching the 15 mixture with a compound of the formula R₂CN, wherein R₂ is as defined above, and allowing the mixture to warm to ambient temperature over a period of about 30 minutes to 1 hour to provide the compound of formula XXXVIII. This method of preparing the compound of formula XXXVIII is preferred for compounds in which R₂ is a nitrogen-containing heteroaryl moiety. Steps 2 and 3 of Scheme 8 illustrate an alternative 20 method of preparing the compound of formula XXXVIII which is preferred for those compounds in which R₂ is a substituted or unsubstituted aryl moiety. In step 2 of Scheme 8, the compound of formula XVI is treated as described in step 1 of Scheme 8 except a compound of the formula R₂C(O)H is substituted for the compound of formula R₂CN, wherein R₂ is as defined above. In step 3 of Scheme 8, the compound 25 of formula XXXIX is oxidized to provide the compound of formula XXXVIII according to methods known to those skilled in the art as described in step 8 of Scheme 1.

The compounds of formula I can also be prepared following one or more synthetic methods that are disclosed in issued patents or published patent applications. In particular, using the intermediates described in Schemes 1-8, referred to above, in 30 particular the intermediates of formulas VIII, X, XI, XVI, and XXIV, those skilled in the art can prepare the compounds of formula I using analogous synthetic methods that have been described for compounds in which a phenyl ring is substituted for the indazole ring in the compounds of formula I. Such analogous synthetic methods are

-27-

disclosed in the following issued patents and published patent applications: United States Patent 5,449,676 (issued September 12, 1995); United States Patent 5,459,151 (issued October 17, 1995); United States Patent 5,491,147 (issued February 13, 1996); European patent application EP 470,805 (published February 12, 1992); European 5 patent application EP 497,564 (published August 5, 1992); European patent application EP 723,962 (published July 15, 1996); WO 92/00968 (published January 23, 1992); WO 93/15044 (published August 5, 1993); WO 93/15045 (published August 5, 1993); WO 93/18024 (published September 16, 1993); WO 93/25517 (published December 10, 1993); WO 94/02465 (published February 3, 1994); WO 95/01338 (published January 12, 1995); WO 95/04045 (published February 9, 1995); WO 95/04046 (published February 9, 1995); WO 95/05386 (published February 23, 1995); WO 95/20578 (published August 3, 1995); WO 95/22520 (published August 24, 1995); WO 15 95/27692 (published October 19, 1995); WO 96/00218 (published January 4, 1996); and WO 96/21435 (published July 18, 1996). The foregoing issued patents and published European and PCT international patent applications are incorporated herein by reference in their entirety.

Specifically, the compounds of formula I wherein R_2 is $-Z_2-R_7$ can be prepared by following analogous synthetic methods disclosed in WO 94/02465, WO 95/01338, WO 93/25517, WO 95/20578, WO 96/00218 and EP 497,564, each of which is referred 20 to above. The compounds of formula I wherein R_2 is R_{10} can be prepared by following analogous synthetic methods disclosed in United States Patent 5,491,147, WO 95/27692 and WO 95/22520, each of which is referred to above. The compounds of formula I wherein R_2 is a substituent of formula (If) or (Ig) can be prepared by following analogous synthetic methods disclosed in WO 95/22520, which is referred to above. 25 The compounds of formula I wherein R_2 is a substituent of formula (Ih) can be prepared by following analogous synthetic methods disclosed in United States Patent 5,459,151, which is referred to above. The compounds of formula I wherein R_2 is $-C(=NOC(O)R_{25})R_{25}$ can be prepared by following analogous synthetic methods disclosed in EP 470,805, which is referred to above. The compounds of formula I 30 wherein R_2 is $-(CR_{17}R_{18})_nNR_9(C(O))_4R_{10}$ can be prepared by following analogous synthetic methods disclosed in WO 92/00968, WO 95/05386, WO 93/15044, and WO 93/15045, each of which is referred to above. The compounds of formula I wherein R_2 is $-CR_{17}R_{18}CHR_{25}NR_9SO_2(CH_2)_nA$, $-CR_{17}R_{18}CHR_{25}NR_9P(O)(OR_{12})C(O)C_1-C_4$ alkyf), or

-CR₁R_{1a}CHR_{2a}NR₆P(O)(C₁-C₄ alkoxy)₂ can be prepared by following analogous synthetic methods disclosed in WO 95/05386, which is referred to above. The compounds of formula I wherein R₂ is a substituent of formula (Ic), (Id) or (Ie) can be prepared by following analogous synthetic methods disclosed in WO 93/18024, which

5 is referred to above. The compounds of formula I wherein R₂ is a substituent of formula (II) can be prepared by following analogous synthetic methods disclosed in EP 723,962, which is referred to above. The compounds of formula I wherein R₂ is -C(=NR₃₂)NH(CH₂)₂(C₆-C₁₀ aryl) can be prepared by following analogous synthetic methods disclosed in WO 96/21435, which is referred to above.

10 The compounds of formula I can be resolved into separate enantiomers by using a chiral LC technique according to the following conditions: column: Chiralcel® OD (250 x 4.6 mm); mobile phase: 50:50:0.1 (Hexane:2-propanol:diethylamine); flow rate: 1 mL/minute; detection: UV (230 nm); temperature: ambient (20-25°C); injection volume: 20 μ L. The compounds of formula I can also be resolved into separate

15 enantiomers according to other techniques familiar to those skilled in the art, including those described in J. March, Advanced Organic Chemistry, (4th Edition, J. Wiley & Sons), 1992, pages 118-125.

The compounds of formula I that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of formula I from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is readily obtained. The desired acid addition salt can also be precipitated from a solution of the free base in an organic solvent by adding to the solution an appropriate mineral or organic acid. Cationic salts of the compounds of formula I are similarly prepared except through reaction of a carboxy group with an appropriate cationic salt reagent such as sodium, potassium, calcium, magnesium, ammonium, N,N'-

dibenzylethylenediamine, N-methylglucamine (meglumine), ethanolamine, tromethamine, or diethanolamine.

For administration to humans in the curative or prophylactic treatment of inflammatory diseases, a variety of conventional routes may be used including orally, 5 parenterally, topically, and rectally (suppositories), in single or divided doses. Oral dosages of a compound of formula I or a pharmaceutically acceptable salt thereof (the "active compounds") are generally in the range of 0.1 to 1000 mg daily for an average adult patient (70 kg), in single or divided doses. Individual tablets or capsules should generally contain from 0.1 to 100 mg of active compound, in a suitable 10 pharmaceutically acceptable vehicle or carrier. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response 15 of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For administration to humans for the inhibition of TNF, a variety of conventional routes may be used including orally, parenterally, topically, and rectally (suppositories), 20 in single or divided doses. In general, the active compound will be administered orally or parenterally at dosages between about 0.1 and 25 mg/kg body weight of the subject to be treated per day, preferably from about 0.3 to 5 mg/kg, in single or divided doses. However, some variation in dosage will necessarily occur depending on the condition 25 of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

For human use, the active compounds of the present invention can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the active 30 compounds can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. The active compounds may be injected parenterally, for example, intravenously, intramuscularly

-30-

or subcutaneously. For parenteral administration, the active compounds are best used in the form of a sterile aqueous solution which may contain other substance; for example, enough salts or glucose to make the solution isotonic.

Additionally, the active compounds may be administered topically when treating 5 inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The therapeutic compounds may also be administered to a mammal other than a human. The dosage to be administered to a mammal will depend on the animal 10 species and the disease or disorder being treated. The therapeutic compounds may be administered to animals in the form of a capsule, bolus, tablet or liquid drench. The therapeutic compounds may also be administered to animals by injection or as an implant. Such formulations are prepared in a conventional manner in accordance with standard veterinary practice. As an alternative the therapeutic compounds may be administered with the animal feedstuff and for this purpose a concentrated feed additive 15 or premix may be prepared for mixing with the normal animal feed.

The ability of the compounds of formula I or the pharmaceutically acceptable salts thereof to inhibit PDE IV may be determined by the following assay.

Thirty to forty grams of human lung tissue is placed in 50 ml of pH 7.4 20 Tris/phenylmethylsulfonyl fluoride (PMSF)/sucrose buffer and homogenized using a Tekmar Tissumizer® (Tekmar Co., 7143 Kemper Road, Cincinnati, Ohio 45249) at full speed for 30 seconds. The homogenate is centrifuged at 48,000 x g for 70 minutes at 4°C. The supernatant is filtered twice through a 0.22 µm filter and applied to a Mono-Q 25 FPLC column (Pharmacia LKB Biotechnology, 800 Centennial Avenue, Piscataway, New Jersey 08854) pre-equilibrated with pH 7.4 Tris/PMSF Buffer. A flow rate of 1 ml/minute is used to apply the sample to the column, followed by a 2 ml/minute flow rate for subsequent washing and elution. Sample is eluted using an increasing, step-wise NaCl gradient in the pH 7.4 Tris/PMSF buffer. Eight ml fractions are collected. Fractions are assayed for specific PDE_{IV} activity determined by [³H]cAMP hydrolysis and the ability of a known PDE_{IV} inhibitor (e.g. rolipram) to inhibit that hydrolysis. 30 Appropriate fractions are pooled, diluted with ethylene glycol (2 ml ethylene glycol/5 ml of enzyme prep) and stored at -20°C until use.

Compounds are dissolved in dimethylsulfoxide (DMSO) at a concentration of 10 mM and diluted 1:25 in water (400 µM compound, 4% DMSO). Further serial dilutions

are made in 4% DMSO to achieve desired concentrations. The final DMSO concentration in the assay tube is 1%. In duplicate the following are added, in order, to a 12 x 75 mm glass tube (all concentrations are given as the final concentrations in the assay tube).

10 The reaction tubes are shaken and placed in a water bath (37°C) for 20 minutes, at which time the reaction is stopped by placing the tubes in a boiling water bath for 4 minutes. Washing buffer (0.5 ml, 0.1M 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (HEPES)/0.1M naci, pH 8.5) is added to each tube on an ice bath. The contents of each tube are filed to an AFF-Gel 601 column (Biorad Laboratories, 15 P.O. Box 1229, 85A Marcus Drive, Melville, New York 11747) (boronate affinity gel, 1 ml bed volume) previously equilibrated with washing buffer. [³H]cAMP is washed with 2 x 6 ml washing buffer, and [³H]5'AMP is then eluted with 4 ml of 0.25M acetic acid. After vortexing, 1 ml of the elution is added to 3 ml scintillation fluid in a suitable vial, vortexed and counted for [³H].

20 % inhibition = $.1 - \frac{\text{average cpm (test compound)} - \text{average cpm (blank)}}{\text{average cpm (control)} - \text{average cpm (blank)}}$

IC_{50} is defined as that concentration of compound which inhibits 50% of specific hydrolysis of $[^3H]cAMP$ to $[^3H]5'AMP$.

The ability of the compounds I or the pharmaceutically acceptable salts thereof to inhibit the production of TNF and, consequently, demonstrate their effectiveness for treating disease involving the production of TNF is shown by the following *in vitro* assay:

Peripheral blood (100 ml) from human volunteers is collected in ethylenediaminetetraacetic acid (EDTA). Mononuclear cells are isolated by FICOLL/Hyphaque and washed three times in incomplete HBSS. Cells are resuspended in a final concentration of 1×10^6 cells per ml in pre-warmed RPMI (containing 5% FCS, glutamine, pen/strep and nystatin). Monocytes are plated as 1×10^6 cells in 1.0 ml in 24-well plates. The cells are incubated at 37°C (5% carbon dioxide) and allowed

to adhere to the plates for 2 hours, after which time non-adherent cells are removed by gentle washing. Test compounds (10 μ l) are then added to the cells at 3-4 concentrations each and incubated for 1 hour. LPS (10 μ l) is added to appropriate wells. Plates are incubated overnight (18 hrs) at 37°C. At the end of the incubation 5 period TNF was analyzed by a sandwich ELISA (R&D Quantikine Kit). IC₅₀ determinations are made for each compound based on linear regression analysis.

The following Examples illustrate the invention. In the following Examples, "min." means minute(s), "psi" means pounds per square inch, "h" means hour(s), "equiv" means equivalent(s), and "conc." means concentrated.

10

PREPARATION 1

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

A. 3-Nitro-4-propyl-benzoic acid. 9.44 g (57.5 mmol, 1.0 equiv) of 4-propylbenzoic acid were partially dissolved in 50 mL concentrated H₂SO₄, and chilled in an ice bath. A solution of 4.7 mL (74.7 mmol, 1.3 equiv) concentrated HNO₃ in 10 15 mL concentrated H₂SO₄, was added dropwise over 1-2 min. After stirring 1 hour at 0°C, the reaction mixture was poured into a 1 L beaker half full with ice. After stirring 10 min., the white solid that formed was filtered, washed 1 x H₂O, and dried to give 12.01 g (100%) of the title compound: mp 106-109°C; IR (KBr) 3200-3400, 2966, 2875, 2887, 2554, 1706, 1618, 1537, 1299, 921 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (t, 3H, J=7.4 Hz), 1.59 (m, 2H), 2.82 (m, 2H), 7.63 (d, 1H, J= 8.0 Hz), 8.12 (dd, 1H, J=1.7, 8.0 Hz), 8.33 (d, 1H, J=1.7 Hz); ¹³C NMR (75.5 MHz, DMSO-d₆) δ 14.2, 23.7, 34.2, 125.4, 130.5, 132.9, 133.6, 141.4, 149.5, 185.9; Anal. calcd for C₁₀H₁₁NO₂•1/4H₂O: C, 58.20; H, 5.42; N, 6.55. Found: C, 58.12; H, 5.31; N, 6.81.

20

B. 3-Amino-4-propyl-benzoic acid. A mixture of 11.96 g (57.2 mmol) 3-nitro-25 4-propyl-benzoic acid and 1.5 g 10% Pd/C, 50% water wet, in 250 mL CH₃OH was placed on a Parr hydrogenation apparatus and shaken under 25 psi H₂ at ambient temperature (20-25°C). After 1 hour, the reaction mixture was filtered through Celite®(trademark)(SiO₂ based filtering agent), and the filtrate concentrated and dried to give 9.80 g (96%) of a pale yellow crystalline solid: mp 139.5-142.5°C; IR (KBr) 3200-2400, 3369, 3298, 2969, 2874, 2588, 1890, 1426, 1260, 916, 864 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (t, 3H, J=7.2 Hz), 1.52 (m, 2H), 2.42 (m, 2H), 5.08 (br s, 2H), 6.96 (d, 1H, J=7.8 Hz), 7.05 (dd, 1H, J=1.7, 7.8 Hz), 7.20 (d, 1H, J=1.7 Hz), MS

(Cl, NH₃) m/z 180 (M+H⁺, base); Anal. calcd for C₁₀H₁₃NO₂•1/3H₂O: C, 64.85; N, 7.89; N, 7.56. Found: C, 64.69; H, 7.49; N, 7.86.

C. 3-Carboxy-6-propyl-benzenediazo t-butyl sulfide. A mixture of 8.80 g (49.1 mmol, 1.0 equiv) 3-amino-4-propyl-benzoic acid and 2.34 g (22.1 mmol, 0.45 equiv) sodium carbonate in 55 mL H₂O was heated gently with a heat gun until mostly dissolved. The reaction mixture was chilled in an ice bath, and a solution of 3.73 g (54.0 mmol, 1.0 equiv) sodium nitrite in 27 mL H₂O was added dropwise. After 15 minutes, the reaction mixture was transferred to a dropping funnel and added over 10 minutes to a beaker containing 55 g of crushed ice and 10.6 mL concentrated HCl. After stirring 10 minutes, the contents of the beaker were transferred to a dropping funnel and added over 5 minutes to a room temperature solution of 5.31 mL (47.1 mmol, 0.96 equiv) t-butyl thiol in 130 mL ethanol. The pH was adjusted to 4.5 by addition of saturated aqueous Na₂CO₃ solution, and the reaction mixture was allowed to stir 1 hour at ambient temperature (20-25°C). 200 mL brine were added, and the mixture was filtered. The solid was washed 1 x H₂O and dried overnight to give 12.25 g (89%) of a brown/rust colored powder (caution-stench): mp 102°C (dec); IR (KBr) 3200-2400, 2962, 2872, 2550, 1678, 1484, 1428, 1298, 1171 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (t, 3H, J=7.3 Hz), 1.48 (m, 2H), 1.55 (s, 9H), 2.42 (m, 2H), 7.29 (d, 1H, J=1.6 Hz), 7.50 (d, 1H, J=8.0 Hz), 7.86 (dd, 1H, J=1.7, 7.9 Hz), 13.18 (br s, 1H); MS (thermospray, NH₄OAc) m/z 281 (M+H⁺, base); Anal. calcd for C₁₄H₂₀N₂O₂S: C, 59.96; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.32; N, 10.02.

D. 3-Ethyl-1H-indazole-8-carboxylic acid. A solution of 12.0 g (42.8 mmol, 1.0 equiv) 3-carboxy-6-propyl-benzenediazo t-butyl sulfide in 150 mL dimethylsulfoxide (DMSO) was added dropwise over 15 minutes to an ambient temperature solution of 44.6 g (398 mmol, 9.3 equiv) potassium tert-butoxide in 200 mL DMSO. After stirring 2 hours at ambient temperature, the reaction mixture was poured into 1.5 L of 0°C 1N HCl, stirred 5 minutes, then extracted 2 x 350 mL ethyl acetate. The ethyl acetate extracts (caution - stench) were combined, washed 2 x 250 mL H₂O, and dried over MgSO₄. Filtration, concentration of filtrate and drying gave a tan solid, which was triturated with 1L of 1:3 Et₂O/Hexanes and dried to give 7.08 g (87%) of a tan crystalline powder: mp 248-251°C; IR (KBr) 3301, 3300-2400, 2973, 2504, 1702, 1455, 1401, 1219 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (t, 3H, J=7.8 Hz), 2.94 (q, 2H, J=7.6 Hz), 7.63 (dd, 1H, J=1.1, 8.4 Hz), 7.81 (d, 1H, J=8.4 Hz), 8.06 (d, 1H, J=1.1 Hz),

12.95 (br s, 1H); MS (Cl, NH₃) m/z 191 (M+H⁺, base); Anal. calcd for C₁₀H₁₀N₂O₂: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.66; H, 5.42; N, 14.80.

E. 3-Ethyl-1H-indazole-6-carboxylic acid methyl ester. 8.78 g (45.8 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in 5 one portion to an ambient temperature solution of 7.92 g (41.6 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid, 16.9 mL (416 mmol, 10 equiv) methanol and 5.59 g (45.8 mmol, 1.1 equiv) dimethylaminopyridine (DMAP) in 250 mL CH₂Cl₂. After 18 hours at room temperature, the reaction mixture was concentrated to 150 mL, diluted with 500 mL ethyl acetate, washed 2 x 100 mL 1N HCl, 1 x 100 mL H₂O, 1 x 100 mL 10 brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 7.8 g of a brown solid, which was purified on a silica gel column (30% to 50% ethyl acetate/hexane gradient) to give 6.41 g (75%) of a tan solid: mp 107-108°C; IR (KBr) 3100-2950, 1723, 1222 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (m, 1H), 7.7-7.8 (m, 2H), 3.96 (s, 3H), 3.05 (q, 2H, J=7.7 Hz), 1.43 (t, 3H, 7.7 Hz); MS (Cl, NH₃) m/z 205 (M+H⁺, base); Anal. calcd for C₁₁H₁₂N₂O₂: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.88; H, 6.01; N, 13.96.

F. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester. 1.17 g (29.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in one portion to an ambient temperature solution of 5.7 g (27.9 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 125 mL anhydrous DMF. After 20 min., 3.89 mL (36.8 mmol, 1.3 equiv) cyclopentyl bromide were added dropwise, and the reaction mixture allowed to stir overnight at room temperature. The mixture was then poured into 1 L H₂O and extracted 3 x 450 mL ethyl acetate. The organic extracts were combined, washed 3 x 400 mL H₂O, 1 x 200 mL brine, and dried over Na₂SO₄. 25 Filtration, concentration of filtrate and drying gave an amber oil, which was purified on a silica gel column (10% ethyl acetate/hexanes, gravity) to give 5.48 g (72%) of a clear oil: ¹H NMR (300 MHz, CDCl₃) δ 8.18 (d, 1H, J=1.0 Hz), 7.7 (m, 2H), 5.00 (quintet, 1H, J=7.5 Hz), 3.97 (s, 3H), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.39 (t, 3H, J=7.6 Hz); HRMS calcd for C₁₆H₂₂N₂O₂: 272.1526. Found: 272.15078.

-35-

G. (1-Cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol. 7 ml (7.0 mmol, 1.0 equiv) lithium aluminum hydride, 1.0 M solution in tetrahydrofuran (THF), were added to a 0°C solution of 1.02 g (7.05 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 50 mL anhydrous THF. After 20 minutes, 1 mL methanol was added cautiously, then the reaction mixture was poured into 500 mL of 5% H₂SO₄ and extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 2 x 40 mL H₂O, 1 x 40 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate, and drying gave 1.58 g of a clear oil, which was purified on a silica gel column to give 1.53 g (89%) clear oil: IR (CHCl₃) 3606, 3411, 3009, 2972, 2875, 1621, 1490 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.65 (d, 1H, J=8.0 Hz) 7.42 (s, 1H), 7.06 (dd, 1H, J=1.0, 8.2 Hz), 4.92 (quintet, 1H, J=7.7 Hz), 4.84 (s, 2H), 2.98 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 3H), 1.38 (t, 3H, J=7.6 Hz); MS (thermospray, NH₄OAc) m/z 245 (M+H⁺, base); HRMS calcd for C₁₅H₂₀N₂O + H: 245.1654. Found: 245.1675.

H. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde. 106 mg (0.301 mmol, 0.05 equiv) tetrapropylammonium perruthenate(VII) were added to a room temperature suspension of 1.47 g (6.02 mmol, 1.0 equiv) (1-cyclopentyl-3-ethyl-1H-indazol-6-yl)-methanol, 1.06 g (9.03 mmol, 1.5 equiv) N-methylmorpholine N-oxide and 3.01 g 4A molecular sieves in 12 mL anhydrous CH₂Cl₂. After 20 minutes the reaction mixture was filtered through a short column of silica gel (eluted with CH₂Cl₂). Fractions containing product were concentrated, and the residue chromatographed on a silica gel column (15% ethyl acetate/hexanes, flash) to give 924 mg (83% of a pale yellow solid: mp 41° C; IR (KBr) 3053, 2968, 2872, 2819, 1695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 10.13 (s, 1H), 7.93 (d, 1H, J=0.9 Hz), 7.77 (d, 1H, J=8.4 Hz), 7.60 (dd, 1H, J=1.2, 8.4 Hz), 5.00 (quintet, 1H, J=7.5 Hz), 3.01 (q, 2H, J=7.8 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.39 (t, 3H, J=7.5 Hz); MS (Cl, NH₃) m/z 243 (M+H⁺, base); Anal. calcd for C₁₆H₁₈N₂O: C, 74.35; H, 7.49; N, 11.58. Found: C, 74.17; H, 7.58; N, 11.79.

PREPARATION 2

1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde

A. 4-Bromo-2-nitro-1-propyl-benzene. 125 g (628 mmol, 1.0 equiv) 1-bromo-4-propyl-benzene were added in one portion to a 10°C solution of 600 mL conc. H₂SO₄ and 200 mL H₂O. With vigorous mechanical stirring, an ambient temperature mixture of 43.2 mL (691 mmol, 1.1 equiv) conc. HNO₃ (69-71%, 16M) in 150 mL conc.

H₂SO₄ and 50 mL H₂O was added dropwise over 30 minutes. The ice bath was allowed to warm to ambient temperature, and the reaction stirred at room temperature for 68 hours. The reaction mixture was poured into a 4 L beaker, loosely packed full with crushed ice. After stirring 1 hour, the mixture was transferred to a 4 L separatory 5 funnel and extracted 4 x 800 mL isopropyl ether. The organic extracts were combined, washed 3 x 800 mL H₂O, 1 x 500 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 150 mL of a yellow liquid, which was purified by silica gel chromatography (2 columns, 3 kg silica gel each, 2% ethyl acetate/hexanes) to afford 63.9 g (42%) of a yellow liquid. The desired regiosomer is 10 the less polar of the two, which are formed in a 1:1 ratio. bp 108°C, 2.0 mm; IR (CHCl₃) 3031, 2966, 2935, 2875, 1531, 1352 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.01 (d, 1H, J=2.1 Hz), 7.62 (dd, 1H, J=2.1, 8.3 Hz) 7.23 (d, 1H, J=8.3 Hz), 2.81 (m, 2H), 1.67 (m, 2H), 0.98 (t, 3H, J=7.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 13.94, 23.74, 34.43, 119.6, 127.4, 133.3, 135.7, 136.4, 149.8; GCMS (EI) m/z 245/243 (M⁺), 147 (base); 15 HRMS calcd for C₉H₁₂NO₂Br + H: 243.9973. Found: 243.9954.

B. 5-Bromo-2-propyl-phenylamine. 121 g (639 mmol, 3.0 equiv) of stannous chloride (anhydrous) were added in one portion to a room temperature solution of 51.9 g (213 mmol, 1.0 equiv) 4-bromo-2-nitro-1-propyl-benzene in 1200 mL absolute ethanol and 12 mL (6 equiv) H₂O. After 24 hours at room temperature, most 20 of the ethanol was removed on a rotary evaporator. The residue was poured into a 4 L beaker, 3/4 full with crushed ice and H₂O. 150 g of NaOH pellets were added portionwise, with stirring, until the pH = 10 and most of the tin hydroxide has dissolved. The mixture was divided in half, and each half extracted 2 x 750 mL ethyl acetate. All four ethyl acetate extracts were combined, washed 1 x 500 mL each 1N NaOH, H₂O, 25 and brine, then dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave a yellow liquid, which was purified on a 1.2 kg silica gel column (1:12 ethyl acetate/hexanes) to give 41.83 g (92%) of a pale yellow liquid: IR (CHCl₃) 3490, 3404, 3008, 2962, 2933, 2873, 1620, 1481 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.8-8.9 (m, 3H), 3.90 (br s, 2H), 2.42 (m, 2H), 1.62 (m, 2H), 0.99 (t, 3H, J=7.3 Hz); GCMS (EI) m/z 30 215/213 (M⁺), 186/184 (base); Anal. calcd for C₉H₁₂NBr: C, 50.49; H, 5.65; N, 6.54. Found: C, 50.77; H, 5.70; N, 6.50.

C. 6-Bromo-3-ethyl-1H-indazole. 49.22 g (230 mmol, 1.0 equiv) 5-bromo-2-propyl-phenylamine were placed in a 3 L flask and chilled in an ice bath. A 0°C solution of 57.5 mL (690 mmol, 3.0 equiv) conc. HCl in 165 mL H₂O was added, and the resulting solid mass which formed was ground up until a fine white suspension resulted. 100 mL more H₂O were added, then a solution of 15.9 g (230 mmol, 1.0 equiv) sodium nitrite in 75 mL H₂O was added dropwise over 10 minutes. The ice bath was removed, and the reaction allowed to stir at room temperature for 30 minutes. The reaction mixture was then filtered through a sintered glass funnel, precooled to 0°C. The filtrate was chilled in an ice bath, and with mechanical stirring, a 0°C solution/suspension of 32.8 g (313 mmol, 1.36 equiv) ammonium tetrafluoroborate in 110 mL H₂O was added dropwise over 10 minutes. The thick white suspension which formed (aryl diazonium tetrafluoroborate salt) was allowed to stir 1.5 hours at 0°C. The mixture was then filtered, and the solid washed 1 x 200 mL 5% aq. NH₄BF₄ (cooled at 0°C), 1 x 150 mL CH₃OH (cooled to 0°C), then 1 x 200 mL Et₂O. Drying at high 15 vacuum, ambient temperature for 1 hour gave 54.47 g (76%) of the diazonium salt, an off-white solid.

1500 mL of ethanol free chloroform were placed in a 3-neck flask, then 34.16 g (348 mmol, 2.0 equiv) potassium acetate (powdered and dried) and 2.3 g (8.7 mmol, 0.05 equiv) 18-crown-6 were added. After 10 minutes, the diazonium salt was added 20 in one portion, and the reaction mixture allowed to stir at room temperature under nitrogen atmosphere for 18 hours. The mixture was then filtered, the solid washed 2 x with CHCl₃, and the filtrate concentrated to give 47 g of crude product (brown crystals). Silica gel chromatography (1.2 kg silica gel, ethyl acetate/hexanes gradient 25 crystals). IR (KBr) 3205, 3008, 2969, 2925, 1616, 1340, 1037 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.86 (br s, 1H), 7.81 (d, 1H, J=1.3 Hz), 7.57 (d, 1H, J=8.4 Hz), 7.24 (dd, 1H, J=1.5, 8.8 Hz), 2.99 (q, 2H, J=7.6 Hz), 1.41 (t, 3H, J=7.6 Hz); MS (Cl, NH₃) m/z 227/225 (M+H⁺, base); Anal. calcd for C₉H₉N₂Br: C, 48.02; H, 4.03; N, 12.45. Found: C, 48.08; H, 3.87; N, 12.45.

D. 6-Bromo-1-cyclopentyl-3-ethyl-1H-indazole. 2.46 g (61.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in 0.5 g portions to a 10°C solution of 13.17 g (58.5 mmol, 1.0 equiv) 6-bromo-3-ethyl-1H-indazole in 500 mL anhydrous DMF. The mixture was stirred at ambient temperature for 20 minutes, then 5 a solution of 8.8 mL (81.9 mmol, 1.4 equiv) cyclopentyl bromide in 10 mL anhydrous DMF was added dropwise. After 18 hours, the reaction mixture was poured into 2 L H₂O and extracted 2 x 1 L ethyl acetate. The organic extracts were combined, washed 2 x 750 mL H₂O, 1 x 500 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 20.7 g of crude product, which was purified on a silica gel 10 column (1.1 kg silica gel, 3% ethyl acetate/hexanes) to give 10.6 g (62%) of an amber liquid: IR (CHCl₃) 2972, 2875, 1606, 1501, 1048 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.56 (d, 1H, J=1.3 Hz), 7.52 (d, 1H, J=8.7 Hz), 7.17 (dd, 1H, J= 1.5, 8.5 Hz), 4.83 (quintet, 1H, J=7.6 Hz), 2.98 (q, 2H, J=7.6 Hz), 2.15 (m, 4H), 2.0 (m, 2H), 1.65 (m, 2H), 1.36 (t, 3H, J=7.7 Hz); MS (thermospray, NH₃OAc) m/z 295/293 (M+H⁺, base); Anal. 15 calcd for C₁₄H₁₇N₂Br: C, 57.35; H, 5.84; N, 9.55. Found: C, 57.48; H, 5.83; N, 9.90.

E. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbaldehyde. 11.6 mL (28.4 mmol, 1.0 equiv) n-BuLi, 2.45 M in hexanes, were added to a -78°C solution of 8.32 g (28.4 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole in 200 mL anhydrous THF. After 30 min. at -78°C, 8.8 mL (114 mmol, 4.0 equiv) anhydrous DMF were added 20 dropwise, and the reaction mixture was allowed to stir an additional 30 minutes at -78°C. The mixture was warmed to room temperature over 1 hour, then 125 mL 1N HCl were added. After stirring for 10 minutes, most of the THF was removed on a rotary evaporator. The residue was diluted with 500 mL H₂O, and extracted 2 x 250 mL ethyl acetate. The organic extracts were combined, washed 1 x 100 mL H₂O, 1 x 100 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying 25 gave a yellow oil, which was purified on silica gel column (15% ethyl acetate/hexanes, gravity) to give 4.70 g (68%) of a yellow crystalline solid: ¹H NMR (300 MHz, CDCl₃) identical to the spectrum of the title compound from Preparation 1.

PREPARATION 3

30 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid

A. 3-Nitro-4-propylbenzoic acid

9.44 g (57.5 mmol, 1.0 equiv) of 4-propylbenzoic acid were partially dissolved in 50 mL conc. H₂SO₄ and chilled in an ice bath. A solution of 4.7 mL (74.7 mmol, 1.3

equiv) conc. HNO_3 in mL conc. H_2SO_4 was added dropwise over 1-2 minutes. After stirring 1 hour at 0°C, the reaction mixture was poured into a 1 L beaker half full with ice. After stirring 10 minutes, the white solid which formed was filtered, washed 1 x H_2O , and dried to give 12.01 g (100%) of the title compound: mp 106-109°C; IR (KBr) 5 3200-3400, 2966, 2875, 2667, 2554, 1706, 1618, 1537, 1299, 921 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, 3H, $J=7.4$ Hz), 1.59 (m, 2H), 2.82 (m, 2H), 7.63 (d, 1H, $J=8.0$ Hz), 8.12 (dd, 1H, $J=1.7, 8.0$ Hz), 8.33 (d, 1H, $J=1.7$ Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 14.2, 23.7, 34.2, 125.4, 130.5, 132.9, 133.6, 141.4, 149.5, 165.9; Anal. calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_4 \cdot 1/4\text{H}_2\text{O}$: C, 56.20; H, 5.42; N, 6.55. Found: C, 56.12; H, 5.31; N, 6.81.

10 B. 3-Amino-4-propyl-benzoic acid

A mixture of 11.96 g (57.2 mmol) 3-nitro-4-propyl-benzoic acid and 1.5 g 10% Pd/C, 50% water wet, in 250 mL CH_3OH was placed on a Parr hydrogenation apparatus and shaken under 25 psi H_2 at ambient temperature. After 1 h, the reaction mixture was filtered through Celite®, and the filtrate concentrated and dried to give 9.80 g (96%) of a pale yellow crystalline solid: mp 139.5-142.5°C; IR (KBr) 3200-2400, 3369, 3298, 2969, 2874, 2588, 1690, 1426, 1260, 916, 864 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ 0.90 (t, 3H, $J=7.2$ Hz), 1.52 (m, 2H), 2.42 (m, 2H), 5.08 (br s, 2H), 6.96 (d, 1H, $J=7.8$ Hz), 7.05 (dd, 1H, $J=1.7, 7.8$ Hz), 7.20 (d, 1H, $J=1.7$ Hz); MS (Cl, NH_3) m/z 180 ($\text{M}+\text{H}^+$, base); Anal. calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2 \cdot 1/3\text{H}_2\text{O}$: C, 64.85; N, 7.89; N, 7.56. Found: 20 C, 64.89; H, 7.49; N, 7.88.

C. 3-Carboxy-8-propyl-benzenediazo t-butyl sulfide

A mixture of 8.80 g (49.1 mmol, 1.0 equiv) 3-amino-4-propyl-benzoic acid and 2.34 g (22.1 mmol, 0.45 equiv) sodium carbonate in 55 mL H_2O was heated gently with a heat gun until most dissolved. The reaction mixture was chilled in an ice bath, and 25 a solution of 3.73 g (54.0 mmol, 1.0 equiv) sodium nitrite in 27 mL H_2O was added dropwise. After 15 minutes, the reaction mixture was transferred to a dropping funnel and added over 10 minutes to a beaker containing 55 g of crushed ice and 10.6 mL conc. HCl. After stirring 10 minutes, the contents of the beaker were transferred to a dropping funnel and added over 5 minutes to a room temperature solution of 5.31 mL (47.1 mmol, 0.96 equiv) t-butyl thiol in 130 mL ethanol. The pH was adjusted to 4-5 by addition of saturated aqueous Na_2CO_3 solution, and the reaction mixture was allowed to stir 1 hour at ambient temperature. 200 mL brine were added, and the mixture was filtered. The solid was washed 1 x H_2O and dried overnight to give 12.25

g (89%) of a brown/rust colored powder (caution - stench): mp 102°C (dec); IR (KBr) 3200-2400, 2962, 2872, 2550, 1678, 1484, 1428, 1298, 1171 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.84 (t, 3H, J=7.3 Hz), 1.48 (m, 2H), 1.55 (s, 9H), 2.42 (m, 2H), 7.29 (d, 1H, J=1.6 Hz), 7.50 (d, 1H, J=8.0 Hz), 7.86 (dd, 1H, J=1.7, 7.9 Hz), 13.18 (br s, 1H);

5 MS (thermospray, NH₄OAc) m/z 281 (M+H⁺, base); Anal. calcd for C₁₄H₂₀N₂O₂S: C, 59.96; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.32; N, 10.02.

D. 3-Ethyl-1H-indazole-6-carboxylic acid

A solution of 12.0 g (42.8 mmol, 1.0 equiv) 3-carboxy-6-propyl-benzenediazo t-butyl sulfide in 150 mL DMSO was added dropwise over 15 minutes to a room 10 temperature solution of 44.6 g (398 mmol, 9.3 equiv) potassium t-butoxide in 200 mL DMSO. After stirring 2 hours at ambient temperature, the reaction mixture was poured into 1.5 L of 0°C 1N HCl, stirred 5 minutes, then extracted 2 x 350 mL ethyl acetate. The ethyl acetate extracts (caution-stench) were combined, washed 2 x 250 mL H₂O, and dried over MgSO₄. Filtration, concentration of filtrate and drying gave a tan solid, 15 which was triturated with 1 L of 1:3 Et₂O/Hexanes and dried to give 7.08 g (87%) of a tan crystalline powder: mp 248-251°C; IR (KBr) 3301, 3300-2400, 2973, 2504, 1702, 1455, 1401, 1219 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 1.31 (t, 3H, J=7.6 Hz), 2.94 (q, 2H, J=7.6 Hz), 7.63 (dd, 1H, J=1.1, 8.4 Hz), 7.81 (d, 1H, J=8.4 Hz), 8.06 (d, 1H, J=1.1 Hz), 12.95 (br s, 1H); MS (Cl, NH₃) m/z 191 (M+H⁺, base); Anal. calcd for 20 C₁₀H₁₆N₂O₂: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.66; H, 5.42; N, 14.80.

E. 3-Ethyl-1H-indazole-6-carboxylic acid methyl ester

8.78 g (45.8 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to a room temperature solution of 7.92 g (41.6 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid, 18.9 mL (416 mmol, 10 equiv) 25 methanol and 5.59 g (45.8 mmol, 1.1 equiv) DMAP in 250 mL CH₂Cl₂. After 18 hours at room temperature, the reaction mixture was concentrated to ~150 mL, diluted with 500 mL ethyl acetate, washed 2 x 100 mL 1N HCl, 1 x 100 mL H₂O, 1 x 100 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 7.8 g of a brown solid, which was purified on a silica gel column (30% to 50% ethyl 30 acetate/hexanes gradient) to give 6.41 g (75%) of a tan solid: mp 107-108°C; IR (KBr) 3100-2950, 1723, 1222 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (m, 1H), 7.7-7.8 (m, 2H), 3.98 (s, 3H), 3.05 (q, 2H, J=7.7 Hz), 1.43 (t, 3H, 7.7 Hz); MS (Cl, NH₃) m/z 205

-41-

(M+H⁺, base); Anal. calcd for C₁₁H₁₂N₂O₂: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.88; H, 6.01; N, 13.96.

F. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

1.17 g (29.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added 5 in one portion to a room temperature solution of 5.7 g (27.9 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 125 mL anhydrous DMF. After 20 minutes, 3.89 mL (36.6 mmol, 1.3 equiv) cyclopentyl bromide were added dropwise, and the reaction mixture allowed to stir overnight at room temperature. The mixture was then poured into 1 L H₂O and extracted 3 x 400 mL H₂O, 1 x 200 mL brine, and 10 dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave an amber oil, which was purified on a silica gel column (10% ethyl acetate/hexanes, gravity) to give 5.48 g (72%) of a clear oil: ¹H MR (300 MHz, CDCl₃) δ 8.16 (d, 1H, J=1.0 Hz), 7.7 (m, 2H), 5.00 (quintet, 1H, J=7.5 Hz), 3.97 (s, 3H), 3.01 (q, 2H, J=7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.39 (t, 3H, J=7.6 Hz); HRMS calc for C₁₆H₂₀N₂O₂: 272.1526. 15 Found: 272.15078.

G. 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid

A mixture of 5.24 g (19.2 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 120 mL methanol and 60 mL 1N NaOH was heated to reflux. After 1 hour, the reaction mixture was cooled to room temperature, 20 concentrated to 75 mL, acidified to pH = 1 with 1N HCl, and extracted 2 x 200 mL ethyl acetate. The organic extracts were combined, washed 1 x 150 mL H₂O, 1 x 150 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 4.79 g (96%) of a white solid. A small sample was recrystallized from ethyl acetate/hexanes to obtain analytical data: mp 157-159°C; IR (KBr) 3100-2500, 1683, 1298 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 13.0 (br s, 1H), 8.21 (s, 1H), 7.79 (d, 1H, J=7.9 Hz), 7.62 (sdd, 1H, J=1.2, 8.4 Hz), 5.18 (quintet, 1H, J=7.5 Hz), 2.92 (q, 2H, J=7.6 Hz), 2.1 (m, 2H), 2.0 (m, 2H), 1.85 (m, 2H), 1.6 (m, 2H), 1.29 (t, 3H, J=7.6 Hz); MS (Cl, NH₃) m/z 259 (M+H⁺, base); Anal. calcd for C₁₅H₁₈N₂O₂: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.77; H, 7.02; N, 10.85.

EXAMPLE 12-Cyclopentyl-2H-indazole-6-carboxylic acid(3,5-dichloro-pyridin-4-yl)amide and1-Cyclopentyl-2H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)amide**1.A 1H-Indazole-6-carboxylic acid**

5 A partial solution of 15.1 g (100 mmol, 1.0 equiv) 3-amino-4-methylbenzoic acid in 150 mL anhydrous THF was added dropwise to a -20°C solution of 18 mL (146 mmol, 1.46 equiv) boron trifluoride etherate in 450 mL ethanol free chloroform. After 5 minutes, 14 mL (106 mmol, 1.06 equiv) of 90% t-butyl nitrite were added dropwise, and the reaction stirred at 0°C for 2 hours. 49 g (500 mmol, 5.0 equiv) potassium acetate were added portionwise, followed by 2.65 g (10 mmol, 0.1 equiv) 18-crown-6 in one portion. The reaction mixture was allowed to stir at room temperature for 48 hours, then was concentrated on a rotary evaporator. 500 mL of 3:7 acetone/ethyl acetate and 150 mL 1N HCl were added, and the mixture stirred for 2 hours. 150 mL brine were added and the mixture was filtered. The filtrate was transferred to a separatory funnel, the layers separated, and the aqueous layer extracted 2 x 100 mL 3:7 acetone/ethyl acetate. The organic layers were combined and dried over MgSO₄. Filtration and concentration of the filtrate gave a solid, to which were added 250 mL of acetic acid. The suspension was heated on a steam bath until mostly dissolved, then was removed from the steam bath and 300 mL of ethereal HCl (prepared by passing 20 HCl (g) through 350 mL Et₂O, chilled in an ice bath, for 10 minutes) were added slowly to the still hot acetic acid solution. 250 mL Et₂O were added and the mixture stirred at room temperature for 1 hour. Filtration and drying gave a golden brown powder. The powder was suspended in 500 mL of 3:7 acetone/ethyl acetate, 100 mL brine were added, and the mixture stirred for 1 hour at room temperature. The layers were 25 separated, and the aqueous layer was extracted 1 x 100 mL ethyl acetate. The combined organic layers were dried over MgSO₄. Filtration, concentration of filtrate and drying at high vacuum, room temperature for 18 hours gave 7.81 g (48%) of a brown powder. mp >275°C; MS (Cl, NH₃) m/z 180 (M+18⁺, base).

1.B 1H-Indazole-6-carboxylic acid methyl ester

30 A mixture of 7.59 g (46.8 mmol, 1.0 equiv) 1H-indazole-6-carboxylic acid in 500 mL CH₃OH and 1 mL conc. H₂SO₄ was heated to reflux for 8 hours, then allowed to stir at room temperature for 18 hours. The mixture was concentrated to ~200 mL, diluted with 1 L ethyl acetate, and washed 1 x 250 mL saturated aqueous NaHCO₃, 1 x 250

mL H₂O, 1 x 250 mL brine, and dried over Na₂SO₄. The aqueous washes were extracted with two portions of ethyl acetate to recover additional product. The organic layers were combined, concentrated, and dried to give 6.75 g (82%) of a yellow-orange-tan solid: ¹H NMR (300 MHz, CDCl₃) δ 10.8 (br s, 1H), 8.28 (dd, 1H, J=0.9, 1.9 Hz), 8.15 (d, 1H, J=1.0 Hz), 7.8 (m, 2H), 3.97 (s, 3H); MS (Cl, NH₃) m/z 177 (M+H⁺, base).

5 1.C 1-Cyclopentyl-1H-indazole-6-carboxylic acid methyl ester and 2-cyclopentyl-2H-indazole-6-carboxylic acid methyl ester

10 1.60 g (39.9 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in one portion to a room temperature solution of 6.70 g (38.0 mmol, 1.0 equiv) 1H-indazole-6-carboxylic acid methyl ester in 150 mL anhydrous DMF. After 30 minutes, 4.5 mL (41.8 mmol, 1.1 equiv) cyclopentyl bromide were added dropwise, and the mixture stirred at room temperature for 24 hours. The reaction mixture was diluted with 1.2 liters of ethyl acetate, washed 3 x 350 mL H₂O, 1 x 250 mL brine, and dried over 15 Na₂SO₄. Filtration, concentration of filtrate and drying gave 12 g of an amber oil, which was purified on a 700 g silica gel column (20% ethyl acetate/hexanes, flash) to give 4.26 g of 1-cyclopentyl-1H-indazole-6-carboxylic acid methyl ester (46% yield, less polar isomer) and 3.66 g of 2-cyclopentyl-2H-indazole-6-carboxylic acid methyl ester (39% yield, more polar isomer). Both compounds were orange oils: data for 1H-indazole regioisomer: IR (CHCl₃) 2996, 2955, 2874, 1717, 1249 cm⁻¹; HRMS calcd for C₁₄H₁₈N₂O₂: 244.1213; found: 244.1209; data for 2H-indazole regioisomer: IR (CHCl₃) 2972, 2955, 2876, 1714, 1242 cm⁻¹; HRMS calcd for C₁₄H₁₈N₂O₂: 244.1213. Found: 244.1220.

25 1.D 1-Cyclopentyl-1H-indazole-6-carboxylic acid

30 A mixture of 3.93 g (16.1 mmol, 1.0 equiv) of 1-cyclopentyl-1H-indazole-6-carboxylic acid methyl ester, 100 mL CH₃OH and 50 mL 1N NaOH was heated to reflux for 30 minutes. The reaction mixture was cooled to room temperature, and most of the CH₃OH removed on a rotary evaporator. The residue was diluted with 325 mL H₂O and acidified to pH = 1 with 2N HCl. After stirring 5 minutes, the mixture was filtered, and the solid washed 2 x H₂O and dried overnight to give 3.42 g (92%) of a yellow powder: mp 172-175°C; Anal. calcd for C₁₃H₁₄N₂O₂: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.62; H, 5.82; N, 12.19.

1.E 2-Cyclopentyl-2H-indazole-6-carboxylic acid

This compound was prepared according to the method of Example 1.D, starting with 3.28 g (13.4 mmol) 2-cyclopentyl-2H-indazole-6-carboxylic acid methyl ester, 100 mL CH₃OH and 40 mL 1N NaOH, to give 2.71 g (88%) of light yellow powder. mp 190-193°C; Anal. calcd for C₁₃H₁₄N₂O₂: C, 67.79; H, 6.13; N, 12.16. Found: C, 67.40; H, 6.04; N, 12.38.

1.F 1-Cyclopentyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl) amide

A suspension of 495 mg (2.15 mmol, 1.0 equiv) 1-cyclopentyl-1H-indazole-6-carboxylic acid, 204 μ L (2.79 mmol, 1.3 equiv) thionyl chloride, and 10 μ L DMF in 10 mL anhydrous toluene was heated to reflux for 3 hours, then cooled to ambient temperature and concentrated to dryness on a rotary evaporator. In a separate flask, a solution of 333 mg (2.04 mmol, 0.95 equiv) 3,5-dichloro-4-aminopyridine in 10 mL anhydrous THF was added dropwise to a 0°C suspension of 198 mg (4.95 mmol, 2.3 equiv) sodium hydride, 60% oil dispersion, in 10 mL anhydrous THF. The mixture was stirred for 15 minutes at room temperature, then was recooled to 0°C. A solution of the acid chloride (prepared above) in 10 mL anhydrous THF was added dropwise, and the reaction mixture allowed to stir at room temperature overnight. 4.5 mL 1N HCl were added dropwise to the reaction mixture, which was then diluted with 200 mL CH₂Cl₂, washed 1 x 30 mL each H₂O, 10% aqueous Na₂CO₃, H₂O, then dried over Na₂SO₄. Purification on a silica gel column (2% CH₃OH/CH₂Cl₂, flash) gave 0.76 g (94%) of product, a yellow amorphous foam: ¹H NMR (300 MHz, CDCl₃) δ 8.58 (s, 2H), 8.19 (d, 1H, J=0.9 Hz), 8.09 (d, 1H, J=0.7 Hz), 7.93 (br s, 1H), 7.84 (dd, 1H, J=0.7, 8.4 Hz), 7.63 (dd, 1H, J=1.4, 8.4 Hz), 5.08 (quintet, 1H), 2.2 (m, 4H), 2.0 (m, 2H), 1.75 (m, 2H); MS (Cl, NH₃) m/z 375 (M+H⁺, base); Anal. calcd for C₁₅H₁₆N₄OCl₂: C, 57.62; H, 4.30; N, 14.93; found: C, 57.68; H, 4.55; N, 14.55.

1.G 2-Cyclopentyl-2H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)amide

This compound was prepared according to the method of Example 1.F, using 424 mg of 2-cyclopentyl-2H-indazole-6-carboxylic acid as starting material to give 406 mg (59%) of a white amorphous foam: ¹H NMR (300 MHz, CDCl₃) δ 8.57 (s, 2H), 8.36 (d, 1H, J=1.4 Hz), 8.06 (d, 1H, J=0.7 Hz), 7.84 (br s, 1H), 7.78 (dd, 1H, J=0.7, 8.6 Hz), 7.64 (dd, 1H, J=1.5, 8.7 Hz), 5.00 (quintet, 1H), 2.35 (m, 2H), 2.25 (m, 2H), 2.0 (m,

-45-

2H), 1.8 (m, 2H); MS (Cl, NH₃) m/z 375 (M+H⁺, base); Anal. calcd for C₁₆H₁₆N₄OCl₂: C, 57.62; H, 4.30; N, 14.93. Found: C, 57.39; H, 4.59; N, 14.56.

EXAMPLE 2

3-Nitro-4-propyl-benzoic acid

5 9.44 g (57.5 mmol, 1.0 equiv) of 4-propylbenzoic acid were partially dissolved in 50 mL conc. H₂SO₄ and chilled in an ice bath. A solution of 4.7 mL (74.7 mmol, 1.3 equiv) conc. HNO₃ in 10 mL conc. H₂SO₄ was added dropwise over 1-2 min. After stirring 1 h at 0°C, the reaction mixture was poured into a 1 L beaker half full with ice. After stirring 10 min., the white solid which formed was filtered, washed 1 x H₂O, and dried to give 12.01 g (100%) of the title compound: mp 106-109°C; IR (KBr) 3200-3400, 2966, 2875, 2667, 2554, 1706, 1618, 1537, 1299, 921 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (t, 3H, J=7.4 Hz), 1.59 (m, 2H), 2.82 (m, 2H), 7.63 (d, 1H, J=8.0 Hz), 8.12 (dd, 1H, J=1.7, 8.0 Hz), 8.33 (d, 1H, J=1.7 Hz); ¹³C NMR (75.5 MHz, DMSO-D₆) δ 14.2, 23.7, 34.2, 125.4, 130.5, 132.9, 133.6, 141.4, 149.5, 165.9; Anal. calcd for 10 C₁₀H₁₁NO₄·1/4H₂O: C, 56.20; H, 5.42; N, 6.55. Found: C, 56.12; H, 5.31; N, 6.81.

15

EXAMPLE 3

3-Amino-4-propyl-benzoic acid

20 A mixture of 11.96 g (57.2 mmol) 3-nitro-4-propyl-benzoic acid and 1.5 g 10% Pd/C, 50% water wet, in 250 mL CH₃OH was placed on a Parr hydrogenation apparatus and shaken under 25 psi H₂ at ambient temperature. After 1 h, the reaction mixture was filtered through Celite®, and the filtrate concentrated and dried to give 9.80 g (96%) of a pale yellow crystalline solid: mp 139.5-142.5°C; IR (KBr) 3200-2400, 3369, 3298, 2969, 2874, 25588, 1690, 1426, 1260, 916, 864 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 0.90 (t, 3H, J=7.2 Hz), 1.52 (m, 2H), 2.42 (m, 2H), 5.08 (br s, 2H), 6.96 (d, 1H, J=7.8 Hz), 7.05 (dd, 1H, J=1.7, 7.8 Hz), 7.20 (d, 1H, J=1.7 Hz); MS (Cl, NH₃) m/z 180 (M+H⁺, base); Anal. calcd for C₁₀H₁₃NO₂·1/3H₂O: C, 64.85; N, 7.89; N, 7.56. Found: C, 64.69; H, 7.49; N, 7.86.

25

EXAMPLE 4

3-Carboxy-6-propyl-benzenediazo t-butyl sulfide

30 A mixture of 8.80 g (49.1 mmol, 1.0 equiv) 3-amino-4-propyl-benzoic acid and 2.34 g (22.1 mmol, 0.45 equiv) sodium carbonate in 55 mL H₂O was heated gently with a heat gun until mostly dissolved. The reaction mixture was chilled in an ice bath, and a solution of 3.73 g (54.0 mmol, 1.0 equiv) sodium nitrite in 27 mL H₂O was added

dropwise. After 15 min., the reaction mixture was transferred to a dropping funnel and added over 10 min. to a beaker containing 55 g of crushed ice and 10.6 mL conc. HCl. After stirring 10 min., the contents of the beaker were transferred to a dropping funnel and added over 5 min. to a room temperature solution of 5.31 mL (47.1 mmol, 0.96 equiv) t-butyl thiol in 130 mL ethanol. The pH was adjusted to 4-5 by addition of saturated aqueous Na_2CO_3 solution, and the reaction mixture was allowed to stir 1 h at ambient temperature. 200 mL brine were added, and the mixture was filtered. The solid was washed 1 x H_2O and dried overnight to give 12.25 g (89%) of a brown/rust colored powder (caution - stench): mp 102°C (dec); IR (KBr) 3200-2400, 2962, 2872, 2550, 1678, 1484, 1428, 1298, 1171 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ 0.84 (t, 3H, $J=7.3$ Hz), 1.48 (m, 2H), 1.55 (s, 9H), 2.42 (m, 2H), 7.29 (d, 1H, $J=1.6$ Hz), 7.50 (d, 1H, $J=8.0$ Hz), 7.86 (dd, 1H, $J=1.7, 7.9$ Hz), 13.18 (br s, 1H); MS (thermospray, NH_4OAc) m/z 281 ($\text{M}+\text{H}^+$, base); Anal. calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$: C, 59.96; H, 7.19; N, 9.99. Found: C, 59.71; H, 7.32; N, 10.02.

15

EXAMPLE 53-Ethyl-1H-indazole-6-carboxylic acid

A solution of 12.0 g (42.8 mmol, 1.0 equiv) 3-carboxy-6-propyl-benzenediazo t-butyl sulfide in 150 mL DMSO was added dropwise over 15 min. to a room temperature solution of 44.6 g (398 mmol, 9.3 equiv) potassium t-butoxide in 200 mL DMSO. After stirring 2 h at ambient temperature, the reaction mixture was poured into 1.5 L of 0°C 1N HCl, stirred 5 min., then extracted 2 x 350 mL ethyl acetate. The ethyl acetate extracts (caution - stench) were combined, washed 2 x 250 mL H_2O , and dried over MgSO_4 . Filtration, concentration of filtrate and drying gave a tan solid, which was triturated with 1 L of 1:3 $\text{Et}_2\text{O}/\text{Hexanes}$ and dried to give 7.08 g (87%) of a tan crystalline powder: mp 248-251 °C; IR (KBr) 3301, 3300-2400, 2973, 2504, 1702, 1455, 1401, 1219 cm^{-1} ; ^1H NMR (300 MHz, DMSO-d_6) δ 1.31 (t, 3H, $J=7.6$ Hz), 2.94 (q, 2H, $J=7.6$ Hz), 7.63 (dd, 1H, $J=1.1, 8.4$ Hz), 7.81 (d, 1H, $J=8.4$ Hz), 8.06 (d, 1H, $J=1.1$ Hz), 12.95 (br s, 1H); MS (Cl, NH_3) m/z 191 ($\text{M}+\text{H}^+$, base); Anal. calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.66; H, 5.42; N, 14.80.

20

EXAMPLE 63-Ethyl-1H-indazole-6-carboxylic acid methyl ester

8.78 g (45.8 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to a room temperature solution of 7.92 g (41.6

mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid, 16.9 mL (416 mmol, 10 equiv) methanol and 5.59 g (45.8 mmol, 1.1 equiv) DMAP in 250 mL CH_2Cl_2 . After 18 h at room temperature, the reaction mixture was concentrated to ~150 mL, diluted with 500 mL ethyl acetate, washed 2 x 100 mL 1N HCl, 1 x 100 mL H_2O , 1 x 100 mL brine, and 5 dried over Na_2SO_4 . Filtration, concentration of filtrate and drying gave 7.8 g of brown solid, which was purified on a silica gel column (30% to 50% ethyl acetate/hexanes gradient) to give 6.41 g (75%) of a tan solid: mp 107-108°C; IR (KBr) 3100-2950, 1723, 1222 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.19 (m, 1H, 7.7-7.8 (m, 2H), 3.96 (s, 3H), 3.05 (q, 2H, J =7.7 Hz), 1.43 (t, 3H, 7.7 Hz); MS (Cl, NH_3) m/z 205 ($\text{M}+\text{H}^+$, base); Anal. 10 calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$: C, 64.70; H, 5.92; N, 13.72. Found: C, 64.88; H, 6.01; N, 13.96.

EXAMPLE 7

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

1.17 g (29.4 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added in one portion to a room temperature solution of 5.7 g (27.9 mmol, 1.0 equiv) 3-ethyl-15 1H-indazole-6-carboxylic acid methyl ester in 125 mL anhydrous DMF. After 20 min., 3.89 mL (36.6 mmol, 1.3 equiv) cyclopentyl bromide were added dropwise, and the reaction mixture allowed to stir overnight at room temperature. The mixture was then poured into 1 L H_2O and extracted 3 x 450 mL ethyl acetate. The organic extracts were combined, washed 3 x 400 mL H_2O , 1 x 200 mL brine, and dried over Na_2SO_4 . 20 Filtration, concentration of filtrate and drying gave an amber oil, which was purified on a silica gel column (10% ethyl acetate/hexanes, gravity) to give 5.48 g (72%) of a clear oil: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (d, 1H, J =1.0 Hz), 7.7 (m, 2H), 5.00 (quintet, 1H, J =7.5 Hz), 3.97 (s, 3H), 3.01 (q, 2H, J =7.6 Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.8 (m, 2H), 1.39 (t, 3H, J =7.6 Hz); HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$: 272.1526. Found: 272.15078.

25

EXAMPLE 8

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid

A mixture of 5.24 g (19.2 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester in 120 mL methanol and 60 mL 1N NaOH was heated to reflux. After 1 h, the reaction mixture was cooled to room temperature, concentrated 30 to 75 mL, acidified to pH = 1 with 1N HCl, and extracted 2 x 200 mL ethyl acetate. The organic extracts were combined, washed 1 x 150 mL H_2O , 1 x 150 mL brine, and dried over Na_2SO_4 . Filtration, concentration of filtrate and drying gave 4.79 g (96%) of a white solid. A small sample was recrystallized from ethyl acetate/hexanes to obtain

analytical data: mp 157-159 °C; IR (KBr) 3100-2500, 1683, 1298 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆) δ 13.0 (br s, 1H, 8.21 (s, 1H), 7.79 (d, 1H, J=7.9 Hz), 7.62 (sdd, 1H, J=1.2, 8.4 Hz), 5.18 (quintet, 1H, J=7.5 Hz), 2.92 (q, 2H, J=7.6 Hz), 2.1 (m, 2H), 2.0 (m, 2H), 1.85 (m, 2H), 1.6 (m, 2H), 1.29 (t, 3H, J=7.6 Hz); MS (Cl, NH₃) m/z 259 (M+H⁺, base); Anal. calcd for C₁₅H₁₈N₂O₂: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.77; H, 7.02; N, 10.85.

EXAMPLE 9

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

10 9.A 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid

7.73 mL (18.9 mmol, 1.0 equiv) n-butyl lithium, 2.45 M in hexanes, were added dropwise to a -78°C solution of 5.55 g (18.9 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole in 100 mL anhydrous THF. After 30 minutes, CO₂ (g) was bubbled into the reaction mixture for 15 minutes. The reaction mixture was warmed to room temperature over several hours, then poured into 600 mL H₂O, acidified to pH = 1, and extracted 2 X 250 mL ethyl acetate. The organic extracts were combined, washed 1 x 150 mL H₂O, 1 x 100 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 4.90 g (100%) of off-white crystals: mp 153-155°C; ¹H NMR (300 MHz, DMSO-d₆) identical with the spectrum of the product from Example 12.

20 9.B 1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride

791 μ L (10.8 mmol, 1.4 equiv) thionyl chloride were added to a room temperature solution of 2.00 g (7.74 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 100 μ L DMF in 100 mL anhydrous toluene. The reaction mixture was heated to reflux for two hours, then cooled to room temperature, concentrated on a rotary evaporator, and dried at high vacuum, room temperature to give 2.16 g (100%) of brown crystals: mp 46-48°C; MS (Cl, NH₃) m/z 279 (M+H⁺, ³⁷Cl), 277 (M+H⁺, ³⁵Cl).

9.C 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

30 This compound was prepared according to the method of example 1.F, using 1.08 g (3.87 mmol) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride as starting material, to give 1.327 g (85%) of pale yellow crystalline solid: mp 174-176°C; MS (Cl,

-49-

NH_3) m/z 405 ($\text{M}+\text{H}^+$, ^{37}Cl), 403 ($\text{M}+\text{H}^+$, ^{35}Cl); Anal. calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{OCl}_2$: C, 59.56; H, 5.00; N, 13.89. Found: C, 60.23; H, 5.42; N, 14.09.

EXAMPLE 10

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (4,6-dichloro-pyrimidin-5-yl)-amide

5 50 μL (0.680 mmol, 1.3 equiv) thionyl chloride were added to a room temperature solution of 135 mg (0.523 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 10 μL DMF in 5 mL anhydrous toluene. The reaction mixture was heated to reflux for 2 hours, then cooled to room temperature, 10 concentrated to dryness on a rotary evaporator, and dried at high vacuum, room temperature for several hours. 21 mg (0.523 mmol, 1.0 equiv) sodium hydride, 60% oil dispersion, were added to a separate flask containing a room temperature solution of 86 mg (0.523 mmol, 1.0 equiv) 5-amino-4,6-dichloro-pyrimidine in 5 mL anhydrous DMF. After 10 minutes, a solution of the acid chloride (prepared above) in 5 mL anhydrous DMF was added, and the mixture stirred for 24 hours at room temperature. 15 The reaction mixture was then heated to 70°C for 1.5 hours, cooled to room temperature, diluted with 75 mL ethyl acetate, washed 2 x 15 mL H_2O , 1 x 16 mL brine, and dried over MgSO_4 . The crude product was purified on a silica gel column (20% ethyl acetate/hexanes) to give 31 mg (15%) of white crystalline solid: mp 171-172°C; 20 Anal. calcd for $\text{C}_{19}\text{H}_{19}\text{N}_5\text{OCl}_2$: C, 56.44; H, 4.74; N, 17.32. Found: C, 56.38; H, 4.76; N, 17.33.

EXAMPLE 11

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid phenylamide

25 46 μL (0.629 mmol, 1.3 equiv) thionyl chloride were added to a room temperature solution of 125 mg (0.484 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 5 μL DMF in 5 mL anhydrous toluene. The reaction mixture was heated to reflux for 2 h, then cooled to room temperature, concentrated to dryness on a rotary evaporator, and dried at high vacuum, room temperature for several hours. The crude acid chloride was dissolved in 5 mL CH_2Cl_2 and added to a 30 room temperature solution of 49 μL (0.532 mmol, 1.1 equiv) aniline and 67 μL (0.484 mmol, 1.0 equiv) triethylamine in 5 mL CH_2Cl_2 . After 18 h at room temperature, the reaction mixture was diluted with 75 mL ethyl acetate, washed 1 x 15 mL each 1N HCl, H_2O , brine, and dried over Na_2SO_4 . Filtration, concentration of filtrate and drying gave

-50-

180 mg of an amber oil, which was purified on a silica gel column to give 160 mg of an off-white solid. Crystallization from ethyl acetate/hexanes gave 130 mg (81%) of a white crystalline solid: mp 146-147°C; Anal. calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.65; H, 7.02; N, 12.55.

5

EXAMPLE 12

4-[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-benzoic acid methyl ester

This compound was prepared according to the method of Example 11, using 300 mg (1.16 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 10 193 mg (1.28 mmol, 1.1 equiv) methyl-4-amino-benzoate as starting materials to give 415 mg (91%) of white crystals: mp 129-132°C; Anal. calcd for $C_{23}H_{25}N_3O_3$: C, 70.56; H, 6.44; N, 10.73. Found: C, 70.36; H, 6.43; N, 10.61.

EXAMPLE 13

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3-chloro-phenyl)-amide

15 This compound was prepared according to the method of Example 11, using 150 mg (0.581 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 68 μ L (0.639 mmol, 1.1 equiv) 3-chloro-aniline as starting materials to give 211 mg (99%) of a clear oil: HRMS calcd for $C_{21}H_{22}N_3OCl + H$: 368.1532. Found: 368.1567.

EXAMPLE 14

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid(3-methoxy-phenyl)-amide

20 87 mg (0.708 mmol, 1.0 equiv) DMAP were added to a room temperature solution of 196 mg (0.708 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride, 99 μ L (0.708 mmol, 1.0 equiv) triethylamine and 80 μ L (0.708 mmol, 1.0 equiv) m-anisidine in 5 mL CH_2Cl_2 . After 48 hours, the reaction mixture was diluted with 75 mL ethyl acetate, washed 2 x 15 mL 1N HCl, 1 x 15 mL H_2O , 1 x 15 mL brine, and dried over $MgSO_4$. Filtration, concentration of filtrate and drying gave 0.27 g of an amber solid, which was purified by silica gel chromatography (ethyl acetate/hexanes gradient 10%, 20%) to give 118 mg of a clear oil. Crystallization from petroleum ether gave 75 mg (29%) of a white powder: mp 91-93°C; Anal. calcd for $C_{22}H_{25}N_3O_2$: C, 72.71; H, 6.95; N, 11.56. Found: C, 72.35; H, 7.15; N, 11.47.

-51-

EXAMPLE 15

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid pyridin-4-ylamide

46 μ L (0.629 mmol, 1.3 equiv) thionyl chloride were added to a room temperature solution of 125 mg (0.484 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 5 μ L DMF in 5 mL anhydrous toluene. The reaction mixture was heated to reflux for 2 hours, then cooled to room temperature, concentrated to dryness on a rotary evaporator, and dried at high vacuum, room temperature for several hours. The crude acid chloride was dissolved in 5 mL anhydrous pyridine, 50 mg (0.532 mmol, 1.1 equiv) 4-aminopyridine were added, and the mixture heated to 40°C for 1 hour. The reaction mixture was cooled to room temperature and allowed to stand overnight. 10 mL H₂O were added, and the mixture was concentrated to dryness on a rotary evaporator. The residue was taken up in 50 mL H₂O and 25 mL CH₂Cl₂, and the layers separated. The aqueous layer was extracted 1 x 25 mL CH₂Cl₂. The organic extracts were combined, washed 1 x 10 mL each H₂O, brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 133 mg of a white foam, which was purified on a silica gel column (25% CH₃OH/CH₂Cl₂) to give 122 mg of white needles. Recrystallization from ethyl acetate/hexanes gave 101 mg (62%) of white shiny plates: mp 144-146°C; Anal. calcd for C₂₀H₂₂N₄O: C, 71.83; H, 6.63; N, 16.75. Found: C, 72.00; H, 7.03; N, 16.16.

EXAMPLE 16

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid pyridin-3-ylamide

This compound was prepared according to the method of Example 15, using 58 mg (0.210 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride and 22 mg (0.231 mmol, 1.1 equiv) 3-aminopyridine as starting materials, to give 24 mg (34%) of white crystals: mp 133-135°C; HRMS calcd for C₂₀H₂₂N₄O + H: 335.1872. Found: 335.1800.

EXAMPLE 17

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid pyridin-2-ylamide

This compound was prepared according to the method of Example 15, using 49 mg (0.177 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride and 18 mg (0.195 mmol, 1.1 equiv) 2-aminopyridine as starting materials, to give 17 mg (34%) of yellow amorphous foam: HRMS calcd for C₂₀H₂₂N₄O + H: 335.1872. Found: 335.1874.

-52-

EXAMPLE 18

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (pyridin-4-ylmethyl)-amide

This compound was prepared according to the method of Example 15, using 51 mg (0.184 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride and 5 20 μ L (0.193 mmol, 1.05 equiv) 4-(aminomethyl)pyridine as starting materials, to give 13 mg (20%) of white crystals: mp 147-149°C; HRMS calcd for $C_{21}H_{24}N_4O + H$: 349.2028. Found: 349.2031.

EXAMPLE 19

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid(2-pyridin-4-yl-ethyl)-amide

10 This compound was prepared according to the method of Example 15, using 78 mg (0.282 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride and 36 μ L (0.295 mmol, 1.05 equiv) 4-(2-aminoethyl)pyridine as starting materials, to give 35 mg (35%) of white crystals: mp 123-126°C; Anal. calcd for $C_{22}H_{28}N_4O \cdot 1/4H_2O$: C, 72.01; H, 7.28; N, 15.27. Found: C, 71.77; H, 7.45; N, 15.23.

15 EXAMPLE 20

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid quinolin-5-ylamide

This compound was prepared according to the method of Example 15, using 91 mg (0.329 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl chloride and 52 mg (0.362 mmol, 1.1 equiv) 5-amino-quinoline as starting materials, to give 20 38 mg (30%) of pale yellow powder: mp 176-178°C; Anal. calcd for $C_{24}H_{24}N_4O$: C, 74.96; H, 6.29; N, 14.57. Found: C, 74.33; H, 6.53; N, 14.31.

EXAMPLE 21

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid(2,6-dichloro-phenyl)-amide

1.1 mL (15.1 mmol, 1.3 equiv) thionyl chloride were added to a room 25 temperature solution of 3.00 g (11.6 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 150 μ L DMF in 60 mL anhydrous toluene. The reaction mixture was heated to reflux for two hours, then cooled to room temperature, concentrated on a rotary evaporator, and dried at high vacuum, room temperature to give 3.40 g yellow-brown crystals. 1.88 g (11.6 mmol, 1.0 equiv) 2,6-dichloroaniline 30 were added, and the mixture heated in a 200°C oil bath under nitrogen atmosphere. After 15 minutes, the reaction mixture was cooled to room temperature. 75 mL ethyl acetate and 50 mL saturated aqueous NaHCO₃ were added, and the mixture stirred for 10 minutes. The layers were separated, and the organic layer was washed 1 x 20 mL

-53-

saturated NaHCO_3 , 1 x 20 mL H_2O , 1 x 20 mL brine, and dried over Na_2SO_4 . Filtration, concentration of filtrate and drying gave a brown solid, which was recrystallized from ethyl acetate/hexanes to give 3.78 g (81%) of tan crystalline solid: mp 177-179°C; Anal. calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{OCl}_2$: C, 62.69; H, 5.26; N, 10.45. Found: C, 62.67; H, 5.20;

5 N, 10.43.

EXAMPLE 22

4-[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-benzoic acid

A mixture of 380 mg (0.971 mmol, 1.0 equiv) 4-[(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-benzoic acid methyl ester, 4 mL 1N NaOH and 20 mL 10 methanol was heated to reflux for 40 minutes. After cooling to room temperature, the reaction mixture was concentrated on a rotary evaporator, and the residue diluted with 150 mL H_2O , acidified to pH = 1, and extracted 2 x 50 mL ethyl acetate. The organic extracts were combined, washed 1 x 25 mL each H_2O , brine, and dried over Na_2SO_4 . Filtration, concentration of filtrate, and drying at high vacuum, room temperature gave 15 298 mg (81%) of a white crystalline solid: mp 249-251°C; Anal. calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_3$: C, 70.00; H, 6.14; N, 11.13. Found: C, 69.66; H, 6.13; N, 11.08.

EXAMPLE 23

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (4-benzyloxycarbamoyl-phenyl)-amide

20 140 mg (0.728 mmol, 1.1 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to a room temperature solution of 250 mg (0.662 mmol, 1.0 equiv) 4-[(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-benzoic acid, 106 mg (0.662 mmol, 1.0 equiv) O-benzyloxylhydroxylamine hydrochloride, 101 mg (0.662 mmol, 1.0 equiv) 1-hydroxybenzotriazole hydrate, and 194 μL (1.39 mmol, 2.1 equiv) triethylamine in 25 mL CH_2Cl_2 . After 18 hours, the reaction mixture was diluted with 150 mL ethyl acetate, washed 1 x 25 mL each 1N HCl , H_2O , brine, and dried over Na_2SO_4 . The crude product was purified on a silica gel column (2% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$, flash) to give 212 mg (66%) of white crystalline solid: mp 194-198°C; Anal. calcd for $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_3$: C, 72.17; H, 7.10; N, 11.61. Found: C, 71.62; H, 6.47; N, 30 11.85.

EXAMPLE 241-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (4-hydroxycarbamoyl-phenyl)-amide

A mixture of 187 mg (0.387 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (4-benzyloxycarbamoyl-phenyl)-amide and 200 mg 10% Pd/C in 10 mL ethyl acetate and 10 mL methanol was placed on a Parr® hydrogenation apparatus and shaken under 30 psi H₂ at room temperature for 1 hour. The reaction mixture was filtered through Celite®, and the filtrate concentrated and dried to give a tan solid. Purification on a silica gel column (CH₃OH/CH₂Cl₂ gradient 4%, 10%, 20%, flash) gave 10 74 mg (49%) of a tan solid: mp 175°C (dec); HRMS calcd for C₂₂H₂₄N₄O₃ + H: 393.1928. Found: 393.1949.

EXAMPLE 2525.A 1-Cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

This compound was prepared according to the method of Preparation 3, using 15 750 mg (3.67 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 0.38 mL (4.04 mmol, 1.1 equiv) cyclobutyl bromide as starting materials to give 307 mg (32%) of a clear oil: HRMS calcd for C₁₅H₁₈N₂O₂ + H: 259.1447. Found: 259.14550.

25.B 3-Ethyl-1-isopropyl-1H-indazole-6-carboxylic acid methyl ester

This compound was prepared according to the method of Preparation 3, using 20 750 mg (3.67 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 0.38 mL (4.04 mmol, 1.1 equiv) 2-bromopropane as starting materials to give 359 mg (40%) of a clear oil: HRMS calcd for C₁₄H₁₈N₂O₂ + H: 247.1448. Found: 247.14530.

25.C 1-Cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

This compound was prepared according to the method of Preparation 3, using 25 750 mg (3.67 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 0.39 mL (4.04 mmol, 1.1 equiv) cyclopropylmethyl bromide as starting materials to give 338 mg (36%) of a clear oil: HRMS calcd for C₁₅H₁₈N₂O₂ + H: 259.1447. Found 259.1435.

25.D 1-Cyclohex-2-enyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

30 This compound was prepared according to the method of Preparation 3, using 750 mg (3.67 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 0.48 mL (4.04 mmol, 1.1 equiv) 3-bromocyclohexene as starting materials to give 467 mg (45%) of a clear oil: HRMS calcd for C₁₇H₂₀N₂O₂: 284.1525. Found: 284.1512.

25.E 3-Ethyl-1-[6-(4-phenyl-butoxy)-hexyl]-1H-indazole-6-carboxylic acid methyl ester

This compound was prepared according to the method of Preparation 3, using 137 mg (0.671 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 5 273 mg (0.872 mmol, 1.3 equiv) 6-(4-phenyl-butoxy)-hexyl bromide as starting materials to give 163 mg (56%) of a yellow oil: HRMS calcd for $C_{27}H_{36}N_2O_3 + H$: 437.2804. Found 437.2833.

EXAMPLE 26

26.A 1-Cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid

10 This compound was prepared according to the method of Preparation 3, using 225 mg (0.906 mmol, 1.0 equiv) 1-cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester as starting material to give 168 mg (76%) of an off white crystalline solid: mp 148-150°C; HRMS calcd for $C_{14}H_{18}N_2O_2 + H$: 245.1290. Found: 245.1302.

26.B 3-Ethyl-1-isopropyl-1H-indazole-6-carboxylic acid

15 This compound was prepared according to the method of Preparation 3, using 300 mg (1.22 mmol, 1.0 equiv) 3-ethyl-1-isopropyl-1H-indazole-6-carboxylic acid methyl ester as starting material to give 260 mg (92%) of a pale yellow crystalline solid: mp 160-163°C; Anal. calcd for $C_{13}H_{16}N_2O_2$: C, 67.21; H, 6.94; N, 12.05. Found: C, 67.07; H, 7.04; N, 12.16.

20 26.C 1-Cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid

This compound was prepared according to the method of Preparation 3, using 294 mg (1.14 mmol, 1.0 equiv) 1-cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester as starting material to give 261 mg (94%) of a pale yellow crystalline solid: mp 126-130°C; Anal. calcd for $C_{14}H_{18}N_2O_2$: C, 68.83; H, 6.60; N, 11.46. Found:

25 C, 68.39; H, 6.67; N, 11.41.

26.D 3-Ethyl-1-[6-(4-phenyl-butoxy)-hexyl]-1H-indazole-6-carboxylic acid

This compound was prepared according to the method of Preparation 3, using 147 mg (0.337 mmol, 1.0 equiv) 3-ethyl-1-[6-(4-phenyl-butoxy)-hexyl]-1H-indazole-6-carboxylic acid methyl ester as starting material to give 137 mg (96%) of a pale yellow oil: HRMS calcd for $C_{29}H_{34}N_2O_3 + H$: 423.2648. Found: 423.26795.

-56-

EXAMPLE 27

27.A 1-Cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester

A mixture of 417 mg (1.47 mmol, 1.0 equiv) 1-cyclohex-2-enyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester and 50 mg of 10% Pd/C, 50% water wet in 20 mL ethyl acetate was placed on a Parr® hydrogenation apparatus and shaken under 45 psi H₂ for 45 minutes. The reaction mixture was filtered through Celite®, and the filtrate concentrated on a rotary evaporator and dried at high vacuum, room temperature to give 399 mg (95%) of a clear oil: HRMS calcd for C₁₇H₂₂N₂O₂ + H: 287.1759. Found: 287.1783.

10 27.B 1-Cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid

This compound was prepared according to the method of Preparation 3, using 366 mg (1.28 mmol, 1.0 equiv) 1-cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid methyl ester as starting material to give 325 mg (93%) of a pale yellow solid: mp 196-197°C; HRMS calcd for C₁₆H₂₀N₂O₂ + H: 273.1603. Found: 273.1596.

15 EXAMPLE 28

28.A 3-Ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid methyl ester

0.245 mL (2.24 mmol, 2.0 equiv) 1-bromo-4-fluorobenzene were added to a room temperature suspension of 0.23 g (1.12 mmol, 1.0 equiv) 3-ethyl-1H-indazole-6-carboxylic acid methyl ester, 0.23 g (1.67 mmol, 1.5 equiv) potassium carbonate, and ~100 mg (0.348 mmol, 0.3 equiv) Cu₂Br₂ in 6 mL N-methylpyrrolidinone. The reaction mixture was heated to 175°C for 28 hours, then cooled to room temperature, poured into 100 mL H₂O, and extracted 3 x 50 mL ethyl acetate. The organic extracts were combined, washed 2 x 50 mL H₂O, 1 x 50 mL brine. The aqueous washes were back extracted 1 x 75 mL with ethyl acetate. All ethyl acetate extracts were then combined and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 0.6 g of brown oil, which was purified on a silica gel column (10% ethyl acetate/hexanes) to give 96 mg (28%) of a white crystalline solid: mp 72-74°C; MS (Cl, NH₃) m/z 299 (M+H⁺, base).

28.B 3-Ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid

30 This compound was prepared according to the method of Preparation 3, using 96 mg (0.322 mmol, 1.0 equiv) 3-ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid methyl ester as starting material to give 84 mg (92%) of a white solid: mp 204-205°C; HRMS calcd for C₁₆H₁₅N₂O₂F + H: 285.1040. Found: 285.10257.

-57-

EXAMPLE 29

1-Cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

This compound was prepared according to the method of Example 10, using
5 144 mg (0.589 mmol, 1.0 equiv) 1-cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid as
starting material, to give 44 mg (18%) of an off white crystalline solid: mp 166-168°C;
HRMS calcd for $C_{19}H_{18}N_4OCl_2 + H$: 389.0936.

EXAMPLE 30

3-Ethyl-1-isopropyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

This compound was prepared according to the method of Example 10, using
10 232 mg (1.00 mmol, 1.0 equiv) 3-ethyl-1-isopropyl-1H-indazole-6-carboxylic acid as
starting material, to give 73 mg (20%) of an off white crystalline solid: mp 145-148°C;
HRMS calcd for $C_{19}H_{18}N_4OCl_2 + H$: 377.0936. Found: 377.0938.

EXAMPLE 31

1-Cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

This compound was prepared according to the method of Example 10, using
20 224 mg (0.917 mmol, 1.0 equiv) 1-cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic
acid as starting material, to give 51 mg (14%) of an off white crystalline solid: mp 148-
150 °C; HRMS calcd for $C_{19}H_{18}N_4OCl_2 + H$: 389.0936. Found: 389.091.

EXAMPLE 32

1-Cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

25 This compound was prepared according to the method of Example 10, using
300 mg (1.10 mmol, 1.0 equiv) 1-cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid as
starting material, to give 83 mg (18%) of an off white crystalline solid: mp 124-127 °C;
MS(Cl, NH₃) m/z 421 (M+H_{..}, ³⁷Cl+³⁷Cl), 419(M+H_{..}, ³⁵Cl+³⁷Cl, base), 417 (M+H_{..},
³⁵Cl+³⁵Cl).

30

-58-

EXAMPLE 33

3-Ethyl-1-[6-(4-phenyl-butoxy)-hexyl]-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

This compound was prepared according to the method of Example 1, using 127
 5 mg (0.301 mmol, 1.0 equiv) 3-ethyl-1-[6-(4-phenyl-butoxy)-hexyl]-1H-indazole-6-
 carboxylic acid as starting material, to give 119 mg (70%) of a clear oil, which was
 crystallized from ether/hexanes to give 72 mg (42%) of white crystals: mp 76-79°C;
 HRMS calcd for $C_{31}H_{38}N_4O_2Cl_2 + H$: 567.2294. Found: 567.2288

EXAMPLE 34

10 3-Ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide

This compound was prepared according to the method of Example 10, using 80
 mg (0.281 mmol, 1.0 equiv) 3-ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid
 as starting material, to give 22 mg (18%) of a white crystalline solid: mp 197-199 °C;
 15 HRMS calcd for $C_{21}H_{15}N_4OCl_2F + H$: 429.0688. Found: 429.0704.

EXAMPLE 35

[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-acetic acidmethyleneester.

134 mg (0.697 mmol, 1.0 equiv) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
 hydrochloride were added in one portion to a room temperature solution of 180 mg
 20 (0.697 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid, 87.5 mg
 (0.697 mmol, 1.0 equiv) glycine methyl ester hydrochloride, 107 mg (0.697 mmol, 1.0
 equiv) 1-hydroxybenzotriazole hydrate, and 194 μ L (1.39 mmol, 2.0 equiv) triethylamine
 in 5 mL CH_2Cl_2 . After 18 h, the reaction mixture was diluted with 150 mL ethyl acetate,
 washed 1 x 25 mL each 1N HCl, H_2O , brine, and dried over Na_2SO_4 . The crude product
 25 was purified on a silica gel column (40% ethyl acetate/hexanes, flash) to give 187 mg
 (66%) of a white waxy solid: mp 89-93°C; Anal. calcd for $C_{18}H_{23}N_3O_3$; C, 65.63; H, 7.04;
 N, 12.76. Found: C, 65.74; H, 7.02; N, 12.74.

EXAMPLE 36

[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-acetic acid

30 This compound was prepared according to the method of Preparation 3, using
 170mg (0.516mmol, 1.0equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-
 acetic acid methyl ester as starting material to give 155 mg (95%) white crystals: mp

-59-

182-184 °C; Anal. calcd for $C_{17}H_{21}N_3O_3$: C, 64.73; H, 6.71; N, 13.32. Found: C, 64.73; H, 6.80; N, 12.81.

EXAMPLE 37

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (benzyloxycarbamoyl-methyl)-amide

This compound was prepared according to the method of Example 23, using 144mg (0.457 mmol, 1.0 equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-acetic acid as starting material to give 125 mg (65%) of a white amorphous solid: 1H NMR (300 MHz, $CDCl_3$, partial) δ 4.93 (s, 2H), 3.00 (q, 2H, $J=7.6$ Hz), 2.2 (m, 4H), 2.0 (m, 2H), 1.7 (m, 2H), 1.39 (t, 3H, $J=7.6$ Hz); MS (Cl, NH_3) m/z 421 ($M+H_+$, base).

EXAMPLE 38

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethylamide

A mixture of 120 mg (0.285 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (benzyloxycarbamoyl-methyl)-amide and 0.08 g 10% Pd/C, 50% water wet, in 10 mL methanol and 10 mL ethyl acetate was placed on a Parr® hydrogenation apparatus and shaken under 30 psi H_2 at room temperature for 40 minutes. The reaction mixture was filtered through Celite®, and the filtrate concentrated and dried to give 104 mg of a tan solid. Trituration with hexanes gave 69 mg (73%) of a tan crystalline powder: mp 105 °C (dec); HRMS calcd for $C_{17}H_{21}N_3O_3 + H$: 331.1772. Found: 331.1769.

EXAMPLE 39

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-methylsulfanyl-ethyl)-amide

This compound was prepared according to the method of Example 35, using 57 mg (0.221 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 20 mg (0.221 mmol, 1.0 equiv) 2-(methylthio)ethylamine as starting materials. Silica gel chromatography (30% ethyl acetate/hexanes) gave 53 mg (73%) of white crystals: mp 81-83 °C; Anal. calcd for $C_{18}H_{25}N_3O_3$: C, 65.21; H, 7.80; N, 12.68. Found: C, 65.26; H, 7.49; N, 12.81.

-60-

EXAMPLE 40

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (methoxycarbamoyl-methyl)-amide

This compound was prepared according to the method of Example 37, using
5 222mg (0.704 mmol, 1.0 equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-acetic acid and 59 mg (0.704 mmol, 1.0 equiv) methoxylamine hydrochloride as starting materials to give 39 mg of a clear oil, which was crystallized from ether/hexanes to give 34 mg (14%) of white crystals: mp 135-136 °C; Anal. calcd for $C_{18}H_{24}N_4O_3$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.64; H, 6.87; N, 16.47.

10

EXAMPLE 41

3-[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-propionic acid ethyl ester

This compound was prepared according to the method of Example 35, using
297 mg (1.15 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and
15 177 mg (1.15 mmol, 1.0 equiv) *beta*-alanine ethyl ester hydrochloride as starting materials to give 372 mg (90%) of white crystals: mp 74-76 °C; Anal. calcd for $C_{20}H_{27}N_3O_3$: C, 67.21; H, 7.61; N, 11.76. Found: C, 67.40; H, 7.56; N, 11.99.

EXAMPLE 42

3-[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-propionic acid

20 A mixture of 330 mg (0.923 mmol, 1.0 equiv) 3-[(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino]-propionic acid ethyl ester in 10 mL ethanol and 4 mL 1N NaOH was heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was concentrated, diluted with 75 mL H₂O, acidified to pH 1, and extracted 3 x 35 mL ethyl acetate. The organic extracts were combined, washed 1 x 25 mL H₂O, 25 1 x 25 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate on a rotary evaporator and drying at high vacuum, room temperature gave 297 mg (98%) of white solid: mp 151-153 °C; Anal. calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.75; H, 7.12; N, 12.91.

EXAMPLE 43

30 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-benzyloxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 37, using 250 mg (0.759 mmol, 1.0 equiv) 3-[(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-

-61-

amino]-propionic acid and 121 mg (0.759 mmol, 1.0 equiv) O-benzylhydroxylamine hydrochloride as starting materials, to give 237 mg (72%) of a white solid: mp 134-136 °C; Anal. calcd for $C_{25}H_{30}N_4O_3$; C, 69.10; H, 6.96; N, 12.89. Found: C, 69.36; H, 6.75; N, 12.85.

5

EXAMPLE 441-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-hydroxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 38, using 203 mg (0.467 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-benzyloxycarbamoyl-ethyl)-amide as starting material and 50 mg of $Pd(OH)_2/C$ (Pearlman's catalyst) as catalyst, to give 147 mg (91%) of a white powder: mp 166-169 °C; Anal. calcd for $C_{18}H_{24}N_4O_3$; C, 62.77; H, 7.02; N, 16.27. Found: C, 62.58; H, 7.12; N, 16.27.

15

EXAMPLE 45[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-methyl-amino]-acetic acid ethyl ester

This compound was prepared according to the method of Example 35, using 284 mg (1.10 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 169 mg (1.10 mmol, 1.0 equiv) sarcosine ethyl ester hydrochloride as starting materials, to give 220 mg (56%) of a clear oil: Anal. calcd for $C_{20}H_{27}N_3O_3$; C, 67.21; H, 7.61; N, 11.76. Found: C, 66.93; H, 7.73; N, 11.77.

EXAMPLE 46[(1-Cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-methyl-amino]-acetic acid

This compound was prepared according to the method of Example 42, using 201 mg (0.562 mmol, 1.0 equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-methyl-amino]-acetic acid ethyl ester as starting material, to give 185 mg (100%) of a white amorphous solid: Anal. calcd for $C_{18}H_{25}N_3O_3 \cdot 1/4H_2O$; C, 64.74; H, 7.09; N, 12.58. Found: C, 64.73; H, 7.55; N, 12.47.

EXAMPLE 471-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (benzyloxycarbamoyl-methyl)-methyl amide

This compound was prepared according to the method of Example 37, using 160 mg (0.486 mmol, 1.0 equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-methyl-

-62-

amino}-acetic acid as starting material, to give 134 mg (64%) of a clear oil: HRMS calcd for $C_{25}H_{30}N_4O_3 + H$: 435.2398. Found: 435.2376.

EXAMPLE 48

5 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethyl-methyl amide

This compound was prepared according to the method of Example 38, using 126 mg (0.290 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (benzyloxycarbamoyl-methyl)-methyl amide as starting material and 40 mg of Pd(OH)₂/C (Pearlman's catalyst) as catalyst, to give 78 mg (78%) of a light tan powder:
10 mp 63 °C (dec); HRMS calcd for $C_{18}H_{24}N_4O_3 + H$: 345.19285. Found: 345.1912.

EXAMPLE 49

1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid [(hydroxy-methyl-carbamoyl)-methyl]-amide

15 390 mg (16.9 mmol, 20 equiv) sodium, 3 to 8 mm spheres, were added to 10 mL of methanol portion wise for 30 minutes. A solution of 707 mg (8.47 mmol, 10 equiv) N-methylhydroxylamine hydrochloride in 10 mL methanol was added dropwise, and the reaction mixture allowed to stir 10 min. A solution of 279 mg (0.847 mmol, 1.0 equiv) [(1-cyclopentyl-3-ethyl-1H-indazole-6-carbonyl)-amino}-acetic acid methyl ester in 10 mL methanol was added drop wise, and the reaction allowed to stir 16 h at room
20 temperature. The mixture was then concentrated to 1/2 of its initial volume, diluted with 150 mL H₂O, acidified to pH = 2, and extracted 2 x 50 mL ethyl acetate. The organic extracts were combined, washed in 2 x 20 mL, H₂O, 1 x 20 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave 0.33 g of a clear oil, which was purified on a silica gel column (10% CH₃OH/CH₂Cl₂, flash) to give 236 mg of a
25 white foam. Trituration with pentane yielded 150 mg (51%) white amorphous solid: mp 60 °C (dec); Anal. calcd for $C_{18}H_{24}N_4O_3 \cdot H_2O$: C, 59.65; H, 7.23; N, 15.46. Found: C, 62.04; H, 7.39; N, 15.86.

EXAMPLE 50

50.A. S-(1-Benzylloxycarbamoyl-ethyl)-carbamic acid tert-butyl ester

30 This compound was prepared according to the method of Example 44, using 500 mg (2.64 mmol, 1.0 equiv) N-(tert-butoxycarbonyl)-L-alanine and 422 mg (2.64 mmol, 1.0 equiv) O-benzylhydroxylamine hydrochloride, to give 583 mg (75%) of a white oily solid: ¹H NMR (300 MHz, CDCl₃) δ 9.02 (br s, 1H), 7.37 (m, 5H), 4.95 (m,

-63-

1H), 4.90 (s, 2H), 4.03 (m, 1H), 1.41 (s, 9H), 1.33 (d, 3H, J=7.0 Hz); MS (Cl, NH₃) m/z295 (M+H⁺, base).

50.B. S-2-Amino-N-benzyloxy-propionamide hydrochloride.

HCl (g) was bubbled into a 0°C solution of 561 mg (1.91 mmol, 1.0 equiv) S-(1-benzyloxycarbamoyl-ethyl)-carbamic acid tert-butyl ester in 10 mL anhydrous 1,4-dioxane over 1-2 minutes. The reaction mixture was allowed to stir at room temperature for 45 min., then was concentrated on a rotary evaporator and dried at high vacuum, room temperature to give 492 mg (>100%) white hygroscopic amorphous solid: ¹H NMR (300 MHz, DMSO-d₆) δ 11.8 (s, 1H), 8.38 (br s, 3H), 7.38 (m, 5H), 4.82 (m, 2H), 3.68 (m, 1H), 1.29 (d, 3H, J=6.9 Hz).

EXAMPLE 51

S-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-benzyloxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 37, using 200 mg (0.774 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 180 mg (0.774 mmol, 1.0 equiv) S-2-amino-N-benzyloxy-propionamide hydrochloride as starting materials, to give 322 mg (96%) of a clear oil: HRMS calcd for C₂₅H₃₀N₄O₃ + H: 435.2396. Found: 435:2424.

EXAMPLE 52

20 S-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-hydroxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 38, using 288 mg (0.663 mmol, 1.0 equiv) S-1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-benzyloxycarbamoyl-ethyl)-amide as starting material and 90 mg Pd(OH)₂/C as catalyst, to give 170 mg (75%) tan powder: mp 106°C (dec); HRMS calcd for C₁₉H₂₄N₄O₃ + H: 345.1927. Found: 345.1923.

EXAMPLE 53

R-(1-Benzyloxycarbamoyl-ethyl)-carbamic acid tert-butyl ester.

This compound was prepared according to the method of Example 37, using 30 500 mg (2.64 mmol, 1.0 equiv) N-(tert-butoxycarbonyl)-D-alanine and 422 mg (2.64 mmol, 1.0 equiv) O-benzylhydroxylamine hydrochloride, to give 592 mg (76%) of a white oily solid: ¹H NMR (300 MHz, CDCl₃) δ 9.02 (br s, 1H), 7.37 (m, 5H), 4.95 (m,

-64-

1H), 4.90 (s, 2H), 4.03 (m, 1H), 1.41 (s, 9H), 1.33 (d, 3H, J=7.0 Hz); MS (Cl, NH₃) m/z295 (M+H⁺, base).

EXAMPLE 54

5 R-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-hydroxycarbamoyl-ethyl)-amide

54.A. R-2-Amino-N-benzyloxy-propionamide hydrochloride

HCl (g) was bubbled into a 0°C solution of 570 mg (1.94 mmol, 1.0 equiv) R-(1-benzyloxycarbamoyl-ethyl)-carbamic acid tert-butyl ester in 10 mL anhydrous 1,4-dioxane over 1-2 minutes. The reaction mixture was allowed to stir at room 10 temperature for 45 min., then was concentrated on a rotary evaporator and dried at high vacuum, room temperature to give 512 mg (>100%) white hygroscopic amorphous solid: ¹H NMR (300 MHz, DMSO-d₆) δ 11.8 (s, 1H), 8.38 (br s, 3H), 7.38 (m, 5H), 4.82(m, 2H), 3.68 (m, 1H), 1.29 (d, 3H, J=6.9 Hz).

15 54.B. R-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-benzyloxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 37, using 200 mg (0.774 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid and 180 mg (0.774 mmol, 1.0 equiv) R-2-amino-N-benzyloxy-propionamide hydrochloride as starting materials, to give 330 mg (98%) of a clear oil: HRMS calcd for C₂₂H₃₀N₄O₃ 20 + H: 435.2396. Found: 435.2414.

54.C. R-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-hydroxycarbamoyl-ethyl)-amide

This compound was prepared according to the method of Example 30, using 295 mg (0.679 mmol, 1.0 equiv) R-1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid 25 (1-benzyloxycarbamoyl-ethyl)-amide as starting material and 90 mg Pd(OH)₂/C as catalyst, to give 201 mg (86%) tan powder: mp 102°C (dec); HRMS calcd for C₁₉H₂₆N₄O₃ + H: 345.1927. Found: 345.1927.

-65-

EXAMPLE 55

1-Cyclopentyl-3-ethyl-6-thiophen-2-yl-1H-indazole

A solution of 76 mg (0.598 mmol, 1.2 equiv) thiophene-2-boronic acid in 0.5 mL methanol was added to a room temperature suspension of 146 mg (0.498 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole and 17 mg (0.0149 mmol, 0.03 equiv) Pd(PPh₃)₄ in 2 mL toluene and 0.5 mL 2M aqueous Na₂CO₃. The mixture was heated to reflux for 4 h, then cooled to room temperature. The reaction mixture was diluted with 50 mL ethyl acetate, washed 1 x 10 mL each H₂O, brine, and dried over MgSO₄. The crude product was purified on a silica gel column (3% ethylacetate/hexanes, flash) 10 to give 81 mg (55%) of a clear oil, which crystallized on standing: mp 60-64 °C; HRMS calcd for C₁₆H₂₀N₂S + H: 297.1427. Found: 297.1484.

EXAMPLE 56

1-Cyclopentyl-3-ethyl-6-phenyl-1H-indazole

This compound was prepared according to the method of Example 55, using 15 128 mg (0.437 mmol, 1.0 equiv) 6-bromo-1-cyclopentyl-3-ethyl-1H-indazole and 75 mg (0.612 mmol, 1.4 equiv) phenyl boronic acid as starting materials, to give 98 mg (77%) of white crystals: mp 72-74 °C; Anal. calcd for C₂₀H₂₂N₂: C, 82.77; H, 7.64; N, 9.65. Found: C, 81.95; H, 7.82; N, 9.75.

EXAMPLE 57

20 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-methyl-amide

5.2 mg (0.130 mmol, 1.05 equiv) sodium hydride, 60% oil dispersion, were added to a room temperature solution of 50 mg (0.124 mmol, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide in 3 mL anhydrous DMF. After 30 min., 7.7 μ L (0.124 mmol, 1.0 equiv) iodomethane were added and the mixture stirred at room temperature for 4 h. The reaction mixture was diluted with 50 mL H₂O and extracted 2 x 20 mL ethyl acetate. The ethyl acetate extracts were combined, washed 2 x 5 mL H₂O, 1 x 5 mL brine, and dried over Na₂SO₄. Filtration, concentration of filtrate and drying gave a yellow oil, which was purified on 25 a silica gel column (25% ethylacetate/hexanes, flash) to give 27 mg (52%) of a white crystalline solid: mp 118-119 °C; HRMS calcd for C₂₁H₂₂N₄OCl₃ + H: 417.12519. Found: 417.12270.

-66-

EXAMPLE 58

1-Cyclopentyl-3-ethyl-1H-indazole-carboxylic acid dimethyl amide

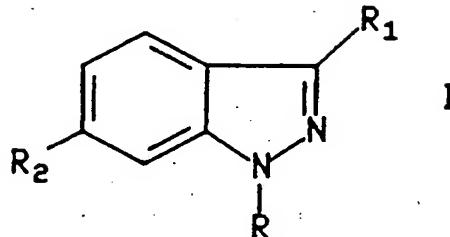
47 mg (0.246 mmol, 1.1. equiv) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added in one portion to a room temperature solution of 57.8 mg (0.224 mmoles, 1.0 equiv) 1-cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid, 18 mg (0.224 mmole, 1.0 equiv) dimethylamine hydrochloride, 34 mg (0.224 mmol, 1.0 equiv) hydroxybenzotriazole hydrate and 66 μ l (0.470 mmol, 2.1 equiv) of triethylamine in 5.0 mL of anhydrous methylene chloride. After stirring the reaction mixture for 18 hours under a N₂ atmosphere, the reaction mixture was diluted with 40 mL of ethylacetate, washed with 10 mL of 1N HCl, water, and brine, and dried over Na₂SO₄. The crude product was purified on a silica gel column (50% EtOAc/50% CH₂Cl₂) to give 55 mg (86%) of clear oil: HRMS calcd for C₁₇H₂₃N₃O + H: 285.1843. Found: 285.1841.

-67-

CLAIMS

What is claimed is:

1. A compound of the formula I



10

or a pharmaceutically acceptable salt thereof, wherein:

R is H, C₁-C₆ alkyl, -(CH₂)_m(5 to 10 membered heterocycl) wherein m is 0 to 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z₁ is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z₂ is O, S, SO₂, or NR₁₂, and wherein said R groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, C₁-C₅ alkyl, C₂-C₅ alkenyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, -CO₂R₁₂, -C(O)NR₁₂R₁₃, -NR₁₂R₁₃ and -SO₂NR₁₂R₁₃;

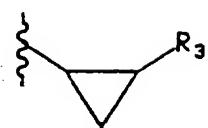
15 R₁ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or phenyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

20 R₂ is R₁₉, -C(O)NR₁₂(CHR₁₂)_mC(O)NR₁₂O(CH₂)_q(C₆-C₁₀ aryl), -C(=NR₃₂)NH(CH₂)_p(C₆-C₁₀ aryl), -C(O)NR₉(CHR₁₂)_mC(O)NR₁₂(CH₂)_pOR₁₂, -C(O)NR₁₂(CHR₁₂)_mS(C₁-C₄ alkyl), -C(=NOC(O)R₂₃)R₂₃, -CR₁₇R₁₈CHR₂₃NR₉SO₂(CH₂)_pA, -CR₁₇R₁₈CHR₂₃NR₉P(O)(OR₁₂)C(O)(C₁-C₄ alkyl), -CR₁₇R₁₈CHR₂₃NR₉P(O)(C₁-C₄ alkoxy)₂, -Z₃R₇, or -(CR₁₇R₁₈)_mNR₉(C(O))_qR₁₀ wherein p is 0 to 2, m is 1 to 6, and q is 1 or 2;

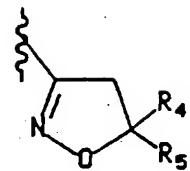
-68-

or R₂ is

5

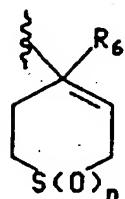


(Ia)

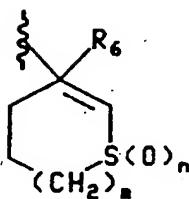


(Ib)

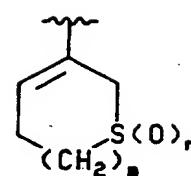
10



(Ic)

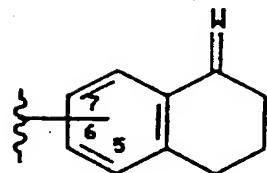


(Id)

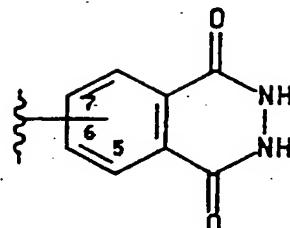


(Ie)

15



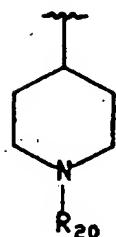
20



(If)

(Ig)

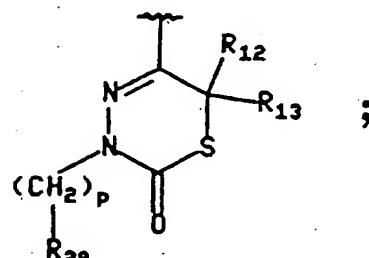
25



or

30

(Ih)



(Ii)

wherein in said formulas (Ia)-(Ii), the structures of formulas (If) and (Ig) are attached to formula I at carbons 5, 6, or 7 of said formulas (If) and (Ig), the dashed line in formulas (Ic) and (Id) indicates a single bond or double bond, except R₆ is absent in formulas (Ic) and (Id) where said dashed line indicates a double bond, n is 0 to 2, p is

5 0 to 6, and m is 0 or 1;

R₃ is -C(O)N(CH₃)(OCH₃) or -(CH₂)_nOH wherein n is 0 to 4;

R₄ and R₅ are independently selected from the group consisting of H, ethyl, -CO₂H and -C(O)NHOH;

10 R₆ is H, cyano, hydroxy, C₁-C₆ alkyl, C₁-C₆ alkoxy, -OC(O)(C₁-C₆ alkyl) or -OC(O)(C₆-C₁₀ aryl);

15 R₇ is C₆-C₁₀ aryl or 5 to 10 membered heterocyclyl, wherein said R₇ groups are optionally substituted by 1 to 3 substituents independently selected from halo, trifluoromethyl, cyano, nitro, -CO₂R₁₂, C₁-C₄ alkoxy, -OC(O)(C₁-C₄ alkyl), -NR₁₂C(O)(C₁-C₄ alkyl), -C(O)NH₂, -C(O)NHOH, -C(O)O(C₁-C₄ alkyl), C₁-C₄ alkyl, -S(O)_nR₁₂ wherein 20 n is 0 to 2, benzoyl, -NR₁₂R₁₃, -OR₁₂, C₁-C₆ alkanoyl, -Y₁(C₆-C₁₀ aryl), -C(O)O(C₆-C₁₀ aryl), -NH(C₆-C₁₀ aryl), -C(O)NH(C₆-C₁₀ aryl), -C(O)NR₁₂O(CH₂)_n(C₆-C₁₀ aryl) wherein n is 1 to 3, and -SO₂NH(C₆-C₁₀ aryl);

R₈ is H, C₁-C₆ alkyl, or -(CH₂)_n(C₆-C₁₀ aryl) wherein n is 0 to 4;

R₉ is H, -OR₁₂, -(CH₂)_mA or -CH₂O(CH₂)_mA wherein m is 0 to 2;

20 R₁₀ is C₁-C₄ alkyl, -OR₁₂, -CR₁₂R₁₃OR₁₂, -CR₁₂R₁₃NR₁₂R₁₃, -CR₁₂(OR₁₃)CR₁₂R₁₃OR₁₂, 2,2-dimethyl-1,3-dioxolan-4-yl, -NR₁₂C(O)NR₁₂R₁₃, -S(CR₁₂R₁₃)_nCH₃ wherein n is 0 to 5, -NR₁₂(CH₂)_q(pyridyl) wherein q is 0 or 1, -P(O)(C₁-C₄ alkoxy)₂, -NR₁₂R₁₃, -NR₁₂OR₁₃, -NR₁₂NR₁₃R₁₁, -NR₁₂CH₂R₁₄, -OCH₂NR₁₂C(O)R₁₄, -OCH₂C(O)NR₁₂R₁₅, -OCHR₁₂OC(O)(C₁-C₄ alkyl), -OCHR₁₂C(O)(C₁-C₃ alkoxy), 25 -O(CH₂)_mR₁₁, or -NR₁₂(CH₂)_mR₁₁ wherein m is 0 to 2;

R₁₁ is H or A;

each R₁₂ and R₁₃ is independently H or C₁-C₄ alkyl;

R₁₄ is methyl or phenyl;

R₁₅ is H, methyl, ethyl, or -CH₂CH₂OH;

30 R₁₆ is H, methyl, ethyl, -CH₂C(O)NH₂, or -CH₂CH₂OH;

each R₁₇ is independently H, hydroxy, cyano, halo, C₁-C₃ alkyl, C₁-C₃ alkoxy, -NR₁₂R₁₃, -C(O)OR₁₂, -C(O)R₁₂, -CH=CR₁₂R₁₃, -C=CR₁₂, -CH₂NR₁₂R₁₃, -CH₂OR₁₂,

-70-

$-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{Y}_2)\text{H}$, or $-\text{CH}_2\text{NR}_{12}\text{C}(\text{O})\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, provided that when R_{17} is hydroxy then R_{18} is H or $\text{C}_1\text{-C}_4$ alkyl;

each R_{18} is independently H, fluoro, cyano, or $\text{C}_1\text{-C}_4$ alkyl, wherein said methyl is optionally substituted by 1 to 3 fluoro substituents;

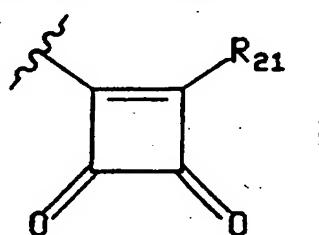
5 or R_{17} and R_{18} are taken together to form an oxo ($=\text{O}$) moiety;

R_{19} is phenyl, naphthyl, pyrrolyl, furanyl, thienyl, oxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, 5,6,7,8-tetrahydroquinolinyl, or 5,6,7,8-tetrahydroisoquinolinyl, wherein said R_{19} groups, except said phenyl, are optionally substituted by 1 to 3 R_{23} substituents, and wherein said phenyl R_{19} group is optionally

10 substituted by 1 to 3 substituents independently selected from R_{23} and R_{24} ;

R_{20} is $-\text{C}(\text{O})\text{R}_{21}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{R}_{21}$, $-\text{C}(\text{O})\text{C}(\text{Y}_2)\text{C}(\text{O})\text{R}_{21}$ or

15



R_{21} is H, $-\text{OR}_{22}$, $-\text{NHR}_{22}$, $-\text{NHOH}$, $-\text{NHNH}_2$, $-(\text{CH}_2)_n\text{Y}_3(\text{phenyl})$ or $-(\text{CH}_2)_n\text{Y}_3(\text{pyridyl})$ wherein n is 0 to 4;

20 R_{22} is H, $\text{C}_1\text{-C}_8$ alkyl, $-(\text{CH}_2)_n\text{Y}_3(\text{phenyl})$ or $-(\text{CH}_2)_n\text{Y}_3(\text{pyridyl})$ wherein n is 0 to 4;

each R_{23} is independently halo, $\text{C}_1\text{-C}_8$ alkyl, $\text{C}_1\text{-C}_7$ alkoxy, $\text{C}_2\text{-C}_8$ alkylenedioxy, trifluoromethyl, $-\text{NR}_{12}\text{R}_{13}$, nitro, $-\text{C}(\text{NR}_{12})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{NOR}_{12})\text{R}_{13}$, $-\text{C}(\text{NCN})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{NCN})\text{SR}_{12}$, $-(\text{CH}_2)_m(\text{CN})$ wherein m is 0 to 3, hydroxy, $-\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{O})\text{NR}_{12}\text{OR}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{NR}_{12}\text{R}_{13}$, $-\text{OC}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{C}(\text{O})\text{R}_{12}$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$,

25 $-\text{CO}_2\text{R}_{12}$, $-\text{SO}_2\text{R}_{12}$, $-\text{SO}_2\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{SO}_2\text{R}_{13}$, or $-\text{NR}_{12}\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$;

each R_{24} is independently imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolidinyl, thiazolidinyl, or imidazolidinyl, wherein each of the foregoing R_{24} substituents is optionally substituted by 1 to 3 R_{23} substituents;

30 R_{25} is $-\text{NR}_{12}\text{R}_{13}$, $-\text{NH}(\text{C}_6\text{-C}_{10} \text{aryl})$, $\text{C}_1\text{-C}_8$ alkoxy, or $\text{C}_6\text{-C}_{10}$ aryloxy;

R_{26} is H, $\text{C}_1\text{-C}_8$ alkyl or $-(\text{CH}_2)_m\text{Y}_4(\text{phenyl})$ wherein m is 0 to 4 and the phenyl moiety of said $-(\text{CH}_2)_m\text{Y}_4(\text{phenyl})$ R_{26} group is optionally substituted by halo, $-\text{OR}_{12}$, $\text{C}_1\text{-C}_8$ alkanoyloxy, $\text{C}_6\text{-C}_{10}$ aryloxy, $-\text{NR}_{12}\text{R}_{13}$, $-\text{NH}(\text{C}_6\text{-C}_{10} \text{aryl})$, or $-\text{NHC}(\text{O})(\text{C}_1\text{-C}_4 \text{ alkyl})$;

each R_{27} is independently halo, $-(CH_2)_pNR_{12}C(O)CH_3$, wherein p is 1 to 5, nitro, cyano, $-NR_{12}R_{13}$, $-CO_2R_{12}$, $-OR_{12}$, $-C(Y_1)NR_{12}R_{13}$, $-NR_{12}C(NCN)S(C_1-C_3$ alkyl), $-NR_{12}C(NCN)NR_{12}R_{13}$, $-NR_{12}C(O)NR_{12}R_{13}$, $-NR_{12}C(O)C(O)NR_{12}R_{13}$, $-C(=NR_{12})NR_{12}R_{13}$, $-S(O)_mCH_3$, wherein m is 0 to 2, $-C(=NR_{12})S(C_1-C_3$ alkyl), $-NR_{12}SO_2(C_1-C_3$ alkyl),

5 $-OC(O)R_{12}$, $-OC(O)NR_{12}R_{13}$, $-NR_{12}SO_2CF_3$, $-NR_{12}C(O)C(O)OR_{12}$, $-NR_{12}C(O)R_{12}$, $-NR_{12}C(O)OR_{12}$, imidazolyl, thiazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

R_{28} is H, fluoro, cyano, or C_1-C_2 alkyl, wherein said alkyl is optionally substituted by 1 to 3 substituents independently selected from halo, $-C(O)NR_{12}R_{13}$, and $-C(O)OR_{12}$;

10 R_{29} is phenyl optionally substituted by 1 or 2 substituents independently selected from $-NR_{12}R_{13}$, nitro, halo, $-OR_{12}$, $-NHR_{30}$, $-NR_{30}R_{31}$, and $-C(O)OR_{12}$;

each R_{30} and R_{31} is independently C_1-C_8 alkyl or C_2-C_8 alkenyl;

15 R_{32} is pyridin-4-yl optionally substituted by 1 or 2 substituents independently selected from halo and C_1-C_4 alkyl;

each A is independently C_1-C_8 alkyl, pyridyl, morpholinyl, piperidinyl, imidazolyl, thienyl, pyrimidyl, thiazolyl, triazolyl, quinolinyl, phenyl, or naphthyl, wherein the foregoing A groups are optionally substituted with 1 to 3 R_{27} substituents, or A is $-(CH_2)_qS(C_1-C_4$ alkyl) wherein q is 1 or 2;

20 W is O, NOH, NNH_2 , $NOC(O)CH_3$, or $NNHC(O)CH_3$;

Y_1 is O or S;

25 Y_2 is O, NOH or H_2 ;

Y_3 is a bond or $-CH=CH-$;

Y_4 is a bond, O, S, or $-NH-$;

Y_5 is O, NR_{12} , NOR_{12} , NCN, $C(CN)_2$, $CR_{12}NO_2$, $CR_{12}C(O)OR_{12}$, $CR_{12}C(O)NR_{12}R_{13}$, $C(CN)NO_2$, $C(CN)C(O)OR_{12}$ or $C(CN)C(O)NR_{12}R_{13}$; and,

30 Z_3 is $-NR_{12}-$, $-(CH_2)_m-$, $-CH_2C(O)NH-$, $-NHCH_2C(O)-$, $-CH_2C(Y_1)CH_2-$, $-CH=CH-$, $-C=C-$, $-CH(Y_1H)-$, $-C(Y_1)-$, $-CH_2C(Y_1)-$, $-C(Y_1)CH_2-$, $-C(Y_1)C(Y_1)-$, $-CH_2NR_{12}-$, $-CH_2-Y_1-$, $-C(Y_1)NR_6(CHR_{12})_n-$, $-NR_6C(Y_1)(CHR_{12})_n-$, $-NHCH_2-$, $-Y_1-CH_2-$, $-SOCH_2-$, $-CH_2SO-$, $-SO_2CH_2-$, $-CH_2SO_2-$, $-OC(Y_1)-$, $-N=N-$, $-NHSO_2-$, $-SO_2NH-$, $-C(Y_1)C(Y_1)NH-$, $-NHC(O)O-$, $-OC(O)NH-$ or $-NHC(O)NH-$, wherein in said Z_3 moieties n is 0 to 4 and m is 1 to 3.

2. The compound of claim 1 wherein R_2 is $-Z_3-R$, wherein Z_3 is $-C(Y_1)NH-$, $-C(O)CH_2-$, $-NHC(Y_1)-$, $-Y_1-CH_2-$, $-OC(O)-$, $-CH=CH-$, or $-C(Y_1)C(Y_1)-$, and R , is an optionally substituted aryl or heteroaryl group selected from phenyl, pyridyl, pyrazinyl,

-72-

thienyl, pyrimidinyl, 2,4-dioxopyrimidin-5-yl, isoxazolyl, isothiazolyl, pyridazinyl, and 1,2,4-triazinyl.

3. The compound of claim 2 wherein R₁ is substituted phenyl, 2,6-dihalo-substituted phenyl, or 3,5-dihalo-pyrid-4-yl.

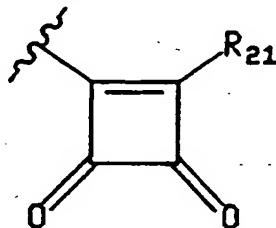
5 4. The compound of claim 1 wherein R₂ is -Z₃-R₇, wherein Z₃ is -C(O)NH(CH₂)_n- or -NHC(O)(CH₂)_n-, wherein n is 0 or 1, and R₇ is phenyl or pyridyl optionally substituted by 1 to 3 substituents independently selected from halo, nitro, trifluoromethyl, -CO₂CH₃, methyl, methoxy, and -C(O)NH₂.

10 5. The compound of claim 1 wherein R₂ is -Z₃-R₇, wherein Z₃ is -C(O)NH- and R₇ is phenyl or pyridyl optionally substituted by 1 to 3 substituents independently selected from halo, C₁-C₄ alkyl, C₁-C₄ alkoxy, cyano, carboxy and -OC(O)(C₁-C₄) alkyl.

6. The compound of claim 1 wherein R₂ is R₁₉, wherein R₁₉ is optionally substituted pyrimidinyl or optionally substituted pyridazinyl.

7. The compound of claim 1 wherein R₂ is a substituent of formula (Ih)
15 wherein R₂₀ is -C(O)R₂₁, -C(O)C(O)R₂₁, or

20



wherein R₂₁ is -OR₂₂, -NHR₂₂, or -NHOH, and R₂₂ is H, C₁-C₃ alkyl, benzyl or pyridylmethyl.

8. The compound of claim 1 wherein R₂ is phenyl substituted by R₂₄
25 wherein said R₂₄ is oxadiazolyl, thiadiazolyl or tetrazolyl wherein said R₂₄ groups are optionally substituted by C₁-C₂ alkyl, or wherein R₂ is phenyl substituted by cyanomethyl, hydroxy or formyl.

9. The compound of claim 1 wherein R₂ is -Z₃-R₇, wherein Z₃ is -C(Y₁)NH-, and R₇ is phenyl, pyrazinyl, pyrimidinyl, isoxazolyl, or pyridyl, wherein each of said R₇ groups is optionally substituted by 1 to 3 substituents independently selected from halo, methoxycarbonyl, trifluoromethyl, benzoyl, acetyl, dimethylamino, hydroxy, nitro, methyl, cyano, methylsulphonyl, and methylthio.

10. The compound of claim 1 wherein R_2 is $-C(=NOC(O)R_{25})R_{26}$ wherein R_{25} is amino and R_{26} is H, C_1 - C_3 alkyl or $-(CH_2)_m$ (phenyl) wherein m is 1 to 4 and said phenyl moiety is optionally substituted by halo, hydroxy, acetoxy, amino or acetamido.

11. The compound of claim 1 wherein R_2 is $-(CR_{17}R_{18})_mNR_9(C(O))_qR_{10}$ wherein m is 2, q is 2, each R_{17} is independently H, cyano or methyl, each R_{18} is independently H or methyl, R_9 is H or methyl, and R_{10} is amino, hydroxy, methoxy or hydroxyamino.

12. The compound of claim 1 wherein R_2 is $-(CR_{17}R_{18})_mNR_9(C(O))_qR_{10}$ wherein m is 2, q is 1, each R_{17} is independently H, $-C(O)NH_2$, $-C=CH$, cyano, formyl, hydroxymethyl, or trifluoromethyl, each R_{18} is independently H or cyano, and R_{10} is C_1 - C_4 alkyl.

13. The compound of claim 1 wherein R_2 is a substituent of formula (Ic), (Id) or (Ie), wherein, in formulas (Ic) and (Id), R_8 is H, hydroxy, C_1 - C_4 alkyl or C_1 - C_4 alkoxy.

14. The compound of claim 1 wherein R_2 is $-C(O)NR_8(CHR_{12})_mC(O)NR_{12}(CH_2)_pOR_{12}$ or $-C(O)NR_{12}(CHR_{12})_mS(C_1-C_4$ alkyl), wherein R_8 , R_{12} , m and p are as defined in claim 1.

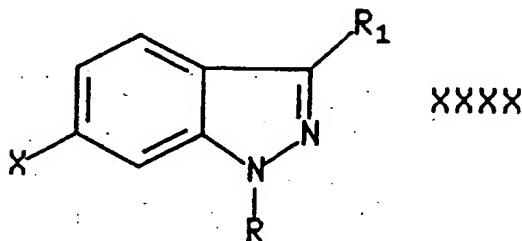
15. The compound of claim 1 selected from the group consisting of
1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2,6-dichloro-phenyl)-amide;
20 1-Cyclobutyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
3-Ethyl-1-isopropyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
1-Cyclopropylmethyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-amide;
1-Cyclohexyl-3-ethyl-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-4-yl)-
25 amide;
3-Ethyl-1-(4-fluoro-phenyl)-1H-indazole-6-carboxylic acid (3,5-dichloro-pyridin-
4-yl)-amide;
1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethyl-amide;
1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (2-methylsulfanyl-ethyl)-amide;
30 1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid hydroxycarbamoylmethyl-methyl
amide;
S-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-benzyloxycarbamoyl-ethyl)-
amide;

-74-

R-1-Cyclopentyl-3-ethyl-1H-indazole-6-carboxylic acid (1-hydroxycarbamoyl-ethyl)-amide; 1-Cyclopentyl-3-ethyl-6-thiophen-2-yl-1H-indazole; 1-Cyclopentyl-3-ethyl-6-phenyl-1H-indazole; and the pharmaceutically acceptable salts of the foregoing compounds.

5 16. A compound of the formula

10



XXXX

or a pharmaceutically acceptable salt thereof, wherein:

R is H, C₁-C₆ alkyl, -(CH₂)_m(5 to 10 membered heterocyclyl) wherein m is 0 to 15 2, (C₁-C₆ alkoxy)C₁-C₆ alkyl, C₂-C₆ alkenyl, or -(Z₁)_b(Z₂)_c(C₆-C₁₀ aryl) wherein b and c are independently 0 or 1, Z₁ is C₁-C₆ alkylene or C₂-C₆ alkenylene, and Z₂ is O, S, SO₂, or NR₁₂, and wherein said R groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of halo, hydroxy, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkoxy, trifluoromethyl, nitro, -CO₂R₁₂, -C(O)NR₁₂R₁₃, -NR₁₂R₁₃ and 20 -SO₂NR₁₂R₁₃;

R₁ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, or phenyl, wherein said alkyl, alkenyl and phenyl R₁ groups are optionally substituted by 1 to 3 substituents independently selected from the group consisting of methyl, ethyl, trifluoromethyl, and halo;

each R₁₂ and R₁₃ is independently H or C₁-C₄ alkyl; and,

25 X is -C(O)Cl.

17. A pharmaceutical composition for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal comprising a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

30 18. A method for the inhibition of phosphodiesterase (PDE) type IV or the production of tumor necrosis factor (TNF) in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

19. A pharmaceutical composition for the prevention or treatment of asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft versus host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, autoimmune diabetes, diabetes insipidus, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, depression, multi-infarct dementia or dermatitis, in a mammal, comprising a therapeutically-effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

20. A method for treating asthma, joint inflammation, rheumatoid arthritis, gouty arthritis, rheumatoid spondylitis, osteoarthritis, and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, HIV, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, multiple sclerosis, type 1 diabetes mellitus, diabetes insipidus, autoimmune diabetes, systemic lupus erythematosus, bronchitis, chronic obstructive airway disease, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease, leukemia, allergic rhinitis, depression, multi-infarct dementia or dermatitis in a mammal which comprises administering to said mammal a therapeutically-effective amount of the compound of claim 1.

INTERNATIONAL SEARCH REPORT

Int'l. Application No.

PCT/IB 97/01023

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 A61K31/415 A61K31/44 C07D409/04 C07D231/56

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>CHEMICAL ABSTRACTS, vol. 125, no. 13, 23 September 1996 Columbus, Ohio, US; abstract no. 167581b, NOMOTO T ET AL: "Preparation of hydroxybenzamide derivatives as prevention and treatment agents for bone diseases" XP002047512 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCE INDEX, vol. 125, 1996, page 1300CS, column 3: compound 180205-98-5!</p>	1-3
X	<p>& JP 08 143 525 A (BANYU PHARMA CO LTD; JAPAN) 4 June 1996</p>	1-3

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

- Special categories of cited documents :

- “A” document defining the general state of the art which is not considered to be of particular relevance
- “E” earlier document but published on or after the international filing date
- “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- “O” document referring to an oral disclosure, use, exhibition or other means
- “P” document published prior to the international filing date but later than the priority date claimed

- T** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X** document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y** document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- Z** document member of the same patent family

2

Date of the actual completion of the international search

Date of mailing of the international search report

20 November 1997

08.12.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-2018

Authorized officer

Fink, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01023

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 444 038 A (JAMES D R ET AL) 22 August 1995 see columns 41-44; table I, the compounds no. 220, 248, and 254 ---	1,4
X	WO 91 17748 A (HOESCH A.-G.; GERMANY) 28 November 1991 see page 26; example 42 ---	1,2
X	EP 0 381 422 A (YAMANOUCHI PHARMACEUTICAL CO., LTD.; JAPAN) 8 August 1990 see page 18; example 22 ---	1
X	CHEMICAL ABSTRACTS, vol. 107, no. 16, 19 October 1987 Columbus, Ohio, US; abstract no. 144822v, SAKAMOTO H ET AL: "Silver halide photographic photosensitive materials" XP002047513 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 7479CS, column 3: compound '110327-54-3' & JP 62 025 747 A (KONISHIROKU PHOTO INDUSTRY CO., LTD.; JAPAN) 3 February 1987 ---	1,2,4
X	CHEMICAL ABSTRACTS, vol. 107, no. 15, 12 October 1987 Columbus, Ohio, US; abstract no. 131065a, ZAKHLENYUK O V ET AL: "Cytophysiological and cytogenetic effects of adenine derivatives in tissue cultures of Haplopappus gracilis" XP002047514 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol 106-115, 1987-1991, page 38538, column 3: compound '110326-95-5' & FIZIOL. RAST. (MOSCOW), vol. 34, no. 3, 1987, pages 584-594, ---	1
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01023

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 14, 5 October 1987 Columbus, Ohio, US; abstract no: 124494n, SAKAMOTO H ET AL: "Silver halide photographic materials" XP002047515 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, page 15104CS, column 2: compound '110325-35-4' & JP 62 050 751 A (KONISHIROKU PHOTO INDUSTRY CO., LTD.; JAPAN) 5 March 1987 ---	1-3
X	EP 0 179 619 A (ICI AMERICAS, INC.; USA) 30 April 1986 see page 44 - page 45; examples 74, 76 ---	1
X	CHEMICAL ABSTRACTS, vol. 102, no. 13, 1 April 1985 Columbus, Ohio, US; abstract no. 113361m, BEYER B ET AL: "Antiallergic activity of some indazole derivatives" XP002047516 see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 11th Collective Index, vol. 96-105, 1982-1986, page 7569CS, column 2: compound '95091-54-6' & ACTA CIENT. VENEZ., vol. 35, no. 2, 1984, pages 103-106, ---	1,4
X	HANNIG E ET AL: "Derivatives of 1-benzyl-6-aminoindazole" PHARMAZIE, vol. 29, no. 10/11, October 1974, pages 685-687, XP002047509 see page 685; table 1, the compounds no. 1-3 ---	1-4
X	ZINNES H ET AL: "1,2-Benzothiazines. 6. 3-Carbamoyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxides as antiinflammatory agents" J. MED. CHEM., vol. 16, no. 1, January 1973, pages 44-48, XP002047510 see page 46; table II, the compound no. 23 ---	1
2		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 97/01023

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DENNLER E B ET AL: "Synthesis of Indazoles Using Polyphosphoric Acid" TETRAHEDRON, vol. 22, no. 9, September 1966, OXFORD GB, pages 3131-3141, XP002047511 see page 3133; table 1, compound no. X see page 3141, line 10 - line 13</p> <p>---</p>	1
X	<p>CHEMICAL ABSTRACTS, vol. 55, no. 26, 25 December 1961 Columbus, Ohio, US; abstract no. 27276h, POZHARSKII ET AL: "Synthesis of N-acylindazoles and 6-acylaminoindazoles with furan nuclei." XP002047517 see abstract & ZHUR. OBSHCHEI KHIM., vol. 31, 1961, pages 1934-1936,</p> <p>---</p>	1
X	<p>GB 747 872 A (IMPERIAL CHEMICAL INDUSTRIES LTD) 14 April 1956 see page 2, column 2; example 1</p> <p>---</p>	1
A	<p>WO 95 01980 A (PFIZER ;DUPLANTIER ALLEN JACOB (US)) 19 January 1995 see the whole document; in particular page 20, example no. 61</p> <p>---</p>	1-20
A	<p>WO 95 27692 A (SMITHKLINE BEECHAM CORP ;BENDER PAUL ELLIOT (US); CHRISTENSEN SIEG) 19 October 1995 cited in the application see the whole document; in particular pages 14-15, example no. 1</p> <p>---</p>	1-20
A	<p>WO 95 22520 A (AMERICAN HOME PROD) 24 August 1995 cited in the application see the whole document; in particular page 17, example no. 7</p> <p>---</p>	1-20
A	<p>WO 95 20578 A (RHONE POULENC RORER LTD ;FENTON GARRY (GB); PALFREYMAN MALCOLM NOR) 3 August 1995 cited in the application see the whole document; in particular pages 58-59, example 10</p> <p>---</p>	1-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 97/01023

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of Invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1-3, 7, 10-13, 17-20

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The present claim 1 is so broad that for determining the scope of a meaningful International Search due account has been taken of Rule 33.3 PCT; special emphasis was put on the following subject-matter: see claims: 4-6, 8, 9, and 14-16

Remark : Although claims 18 and 20 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01023

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 5444038 A	22-08-95	AU 665818 B CN 1079961 A EP 0630367 A HU 70876 A JP 7508259 T MX 9301301 A WO 9318008 A ZA 9301632 A		18-01-96 29-12-93 28-12-94 28-11-95 14-09-95 29-04-94 16-09-93 05-08-94
WO 9117748 A	28-11-91	AT 151633 T AU 662465 B AU 5799294 A AU 649421 B CA 2083179 A CN 1056684 A CS 9101450 A DE 59010701 D EP 0527736 A ES 2102367 T FI 951697 A HR 940696 A HU 64314 A IL 98163 A LT 715 A,B LV 10575 B NO 180118 B NZ 238165 A RU 2084223 C US 5532259 A US 5494911 A		15-05-97 31-08-95 07-07-94 26-05-94 19-11-91 04-12-91 15-01-92 22-05-97 24-02-93 01-08-97 10-04-95 28-02-97 28-12-93 31-01-96 31-01-95 20-04-96 11-11-96 26-08-94 20-07-97 02-07-96 27-02-96
EP 0381422 A	08-08-90	AT 144511 T AU 626980 B AU 4889090 A CA 2008815 A CN 1045583 A,B DE 69028934 D ES 2095855 T HU 9500537 A JP 1900712 C		15-11-96 13-08-92 09-08-90 02-08-90 26-09-90 28-11-96 01-03-97 30-10-95 27-01-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0381422 A		JP 3223278 A JP 6025153 B KR 9311038 B MX 19365 A NO 177007 B PT 93032 B SI 9010198 A RU 2024516 C RU 2059623 C US 5344927 A US 5496942 A	02-10-91 06-04-94 20-11-93 31-01-94 27-03-95 31-01-96 30-06-97 15-12-94 10-05-96 06-09-94 05-03-96
EP 0179619 A	30-04-86	AU 583062 B AU 4881485 A CA 1273934 A DK 479385 A IE 58848 B JP 2015992 C JP 7045466 B JP 61178963 A SU 1545940 A US 5234942 A US 4997844 A SU 1595338 A	20-04-89 24-04-86 11-09-90 20-04-86 17-11-93 19-02-96 17-05-95 11-08-86 23-02-90 10-08-93 05-03-91 23-09-90
GB 747872 A		CH 329376 A FR 1108146 A	09-01-56
WO 9501980 A	19-01-95	AU 6805794 A BR 9406946 A CN 1129940 A CZ 9600036 A EP 0707585 A FI 943208 A HU 74170 A JP 8507084 T MX 9405132 A NO 960056 A PL 312426 A ZA 9404844 A	06-02-95 06-08-96 28-08-96 11-06-97 24-04-96 07-01-95 28-11-96 30-07-96 31-01-95 05-01-96 29-04-96 05-01-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 97/01023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9527692 A	19-10-95	NONE	
WO 9522520 A	24-08-95	AU 1690595 A CA 2182792 A EP 0745063 A FI 963228 A HU 74611 A NZ 279689 A US 5650444 A	04-09-95 24-08-95 04-12-96 16-08-96 28-01-97 22-08-97 22-07-97
WO 9520578 A	03-08-95	AU 1463195 A EP 0741707 A ZA 9500639 A	15-08-95 13-11-96 26-07-96